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BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL.

Vol. VI.—Nos. 52-53.] BALTIMORE, JULY-AUGUST, 1895. [Price, 15 Cents.

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THE TREATMENT OF DIPHTHERIA BY ANTITOXIN.*

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I shall endeavor in this paper, after a brief historical introduction, to present some of the more important general considerations bearing upon the treatment of diphtheria by antitoxic serum, together with statistics of results already reported, with the expectation that those who are to follow in this discussion before the Association will be able to offer the results of personal experience in the application of the new remedy.

In July, 1889, Babès and Lepp, in an article entitled "Recherches sur la Vaccination Antirabiques,"† published results of experiments undertaken to solve the question "whether the fluids and cells of animals which have been rendered by vaccination immune have not become vaccines and capable of protecting also other organisms." The results of these experiments showed that the blood of dogs thoroughly vaccinated against rabies, when injected into susceptible animals, conferred a certain amount of protection against the effects of subsequent inoculation with the rabid virus, and appeared capable of preventing the development of rabies even when the injection of the immune blood was made immediately after the reception of the virus. The authors concluded that "one must admit the possibility of vaccinating with the fluids and cells of animals which have been rendered refractory to the disease."

The first publication clearly demonstrating the principles of serum therapy was made by Behring and Kitasato on December 4, 1890, in an article in the Deutsche medicinische Wochenschrift entitled "Ueber das Zustandekommen der Diphtherie-Immunität und der Tetanus-Immunität bei Thieren." Although in this article the immunizing and curative property of the blood and blood serum of artificially immunized animals was demonstrated only for tetanus, the application of the same principle to diphtheria was indicated in the same article and in a second paper by Behring in the following number of the same journal.

The first public announcement of the demonstration of the power of the blood serum of animals artificially immunized against diphtheria to protect and cure susceptible animals inoculated with the diphtheria bacillus or its poison, was made by Behring in the report of experiments made by himself and Wernicke, and communicated to the Seventh International Congress of Hygiene and Demography held in London in August, 1891. There followed in 1892 the article by Behring and Wernicke,* in which these experiments were fully

* This paper is based upon the address at the opening of the discussion on this subject before the Association of American Physicians at the meeting held in Washington, D. C., May 31, 1895. I have endeavored to bring the paper up to the date of sending it to the printer (July, 1895).

† Babès and Lepp, Annales de l'Institut Pasteur, July, 1889. Richet and Hericourt are sometimes quoted as the first experimenters to show that the blood of animals is capable of conferring protection upon susceptible animals, but their work has no reference to modern serum therapy, as their experiments were made with the blood of dogs which had not previously been vaccinated or treated in any way.

* Behring und Wernicke: Ueber Immunisirung und Heilung von Versuchsthieren bei der Diphtherie. Zeitschrift für Hygiene, Bd. XII.

described and which sets forth the fundamental principles underlying serum therapy of diphtheria.

The first trial of immune serum in the treatment of human diphtheria was made in von Bergmann's clinic in Berlin in the autumn of 1891. This trial, together with those made in 1892 by Henoch in Berlin, by Heubner in Leipzig, and in the Institute for Infectious Diseases in Berlin, were of a tentative nature and made with weak serum and insufficient doses.

It was not until early in 1893 that Behring succeeded in obtaining anti-diphtheric serum equaling the strength of even his so-called normal serum, of which sixty times the strength is that of the weakest Behring's serum at present in use. In April, 1893, Behring referred to 30 cases treated with this normal serum. Of these cases, 11 treated in the Institute for Infectious Diseases were reported in detail by Kossel.

From this period on Behring and Ehrlich succeeded in obtaining healing serum of greater and greater strength, until in August, 1893, Ehrlich and Wassermann obtained from goats healing serum twenty to sixty times the strength of Behring's normal serum. At the Eleventh International Medical Congress held in Rome (March 29 to April 5, 1894) Heubner reported the results of his experience with the serum treatment of human diphtheria. His observations, however, were made on cases treated with much weaker antitoxin than is now recognized as suitable.

In April, 1894, Ehrlich, Kossel and Wassermann reported briefly the results of serum treatment of 220 cases in six Berlin hospitals, the inception of the treatment in these cases dating from June, 1893, but the great majority of the cases occurring after December, 1893. These cases, with additional ones making a total of 233 cases with a mortality of 23 per cent., were reported more fully in an article by Kossel in the Zeitschrift für Hygiene in July, 1894. The era of serum treatment of human diphtheria by approximately sufficient doses of antitoxin really begins with this publication of Ehrlich, Kossel and Wassermann in April, 1894, although even in this series of cases, according to later statements of Ehrlich and Kossel, a large number of the cases were treated with quantities of antitoxin which we now consider to be insufficient.

In an address before the Berlin Medical Society on June 27, 1894, Katz reported the results of antitoxin treatment dating from March 14, 1894, with Aronson's serum from horses on 128 cases of diphtheria in Baginsky's service. In the discussion on this address four weeks later Baginsky completed the series of cases up to 163 with a mortality of 12.9 per cent., and Aronson stated that similarly favorable results had been obtained by Ganghofner in Prague and Escherich in Graz.

In 1893 and the first half of 1894 various articles appeared concerning the preparation of antitoxin, the best methods of estimating its strength, the proper immunizing and therapeutic doses, and similar questions. Since August 1, 1894, Behring's serum prepared at Höchst has been for sale.

It is evident from this brief historical summary that the general principles of serum therapy of diphtheria were fully established and its application to human beings in active operation before Roux delivered his memorable address on the subject at the Eighth International Congress of Hygiene and Demography held in Budapest, September 1–9, 1894, three years after Behring's original communication to the preceding Congress in London. Roux, however, presented the subject with such clearness and force, and with such an array of convincing and carefully analyzed statistical evidence, that the attention of the great body of physicians throughout the world, who had paid little heed to the previous work, was arrested, and the question of the healing power of diphtheria antitoxin became and has continued to be the foremost medical question of the day. From September, 1894, onward the supply of antitoxin from various sources (not all of equally trustworthy character) has become more and more accessible to physicians, and each succeeding month has given birth to a large number of articles on the serum therapy of diphtheria from various parts of the world.

Unless one denies absolutely the causal relation of the Löffler bacillus to diphtheria, it must be admitted that the treatment of this disease by antitoxin rests upon a sound experimental basis. The only notable opponent of the view that the Löffler bacillus is the cause of diphtheria is Hanseman. His arguments, which have been well answered by C. Fraenkel, are equally applicable to the acceptance of the etiological relations of the cholera bacillus, the tubercle bacillus and many other specific bacteria of infectious diseases. It is not probable that any one here sides with Hanseman in this matter, so that it is unnecessary to rehearse the arguments, which in my judgment are conclusive, that the Löffler bacillus is the cause of diphtheria.

The laboratory does not furnish any more impressive experiments than those which demonstrate the power of antitoxic serum to prevent and to cure the disease caused in animals by inoculation with the diphtheria bacillus or its poison. The serum arrests the spread of the local process and abates the symptoms of general toxæmia. These experiments prove beyond question that this healing serum possesses properties which are directly and powerfully antagonistic to the toxic action of the diphtheria bacillus, and there is no good reason to doubt that under similar circumstances this antagonistic power, so readily and surely and uniformly demonstrable in the case of lower animals, will manifest itself also in human beings. The only question, and that of course an important one, in this connection is: To what extent the conditions in the treatment of experimental diphtheria by antitoxin are or can be made similar to those in the therapeutic application of the same agent to human diphtheria?

Although it is true that the lower animals are not susceptible, or only very exceptionally susceptible, to natural infection with the Löffler bacillus, still there is in my opinion identity in essential points, anatomical, clinical and etiological, between experimental diphtheria and uncomplicated human diphtheria. The assertion sometimes made that spreading pseudo-membranous inflammations resembling those of diphtheria cannot be produced experimentally in animals by inoculation with the Löffler bacillus is an error, as I have repeatedly had opportunity to demonstrate by intratracheal inoculations of kittens and rabbits. It is rarely in our power to reproduce experimentally in one species of animal the exact counterpart of a disease caused in another by natural modes of infection,

but in the case of diphtheria the resemblance is closer than in most of our attempts to reproduce such diseases by inoculation of their specific germs.

But even if the anatomical and clinical characters of experimental diphtheria are believed by some to differ more widely than I think they do from those of human diphtheria, there remains as the most important point, regarding the matter here under discussion, the conclusive demonstration that in uncomplicated human diphtheria no less than in experimental diphtheria the local inflammation at the site of infection is caused by the growth of the Löffler bacillus, and the lesions of internal parts and the systemic symptoms are due to the absorption of a toxic substance or of substances formed by this bacillus. It would be difficult to understand why an agent with the specific property of neutralizing in the bodies of animals the effects of these toxic substances should be unable to neutralize in human beings similar effects of the same toxic substances, provided this agent can be administered in the proper dose and at the right time.

Dosage and timely administration are factors of prime importance in determining the efficacy of antitoxic treatment. It is our inability to conform to the demands of these factors which has rendered thus far the treatment of tetanus in human beings by antitoxin disappointing. The tetanus antitoxin can be produced by methods similar to those employed in making the diphtheria antitoxin, and of a power expressed in immunizing units greater than that of the diphtheria antitoxin. No less striking than in diphtheria are the laboratory experiments in the prevention and cure of artificial tetanus by administration of the tetanus antitoxin, but in this case the dose of antitoxin required to check the disease increases so enormously with increase in the size of the animal, on the one hand, and with the lapse of time after reception of the virus on the other hand, that we meet herein most serious obstacles to the successful application of this agent in the treatment of human tetanus.

It has been shown experimentally by Behring, Boer, Roux and others that as regards both of these points the conditions are far more favorable for the treatment of diphtheria by its antitoxin than in the case of tetanus. In an animal, at a certain time after reception of the tetanus poison, the theoretically efficacious dose of the tetanus antitoxin may be a million-fold greater than that required for simple immunization, a quantity too large to administer; whereas the effective dose of the diphtheria antitoxin at relatively the same period may be increased only eight or ten-fold. Doubtless the great advantage which we have in the treatment of human diphtheria by antitoxin as contrasted with tetanus is that we are able to recognize and treat the former disease before the production and absorption of a serious quantity of poison.

Only clinical experience can determine what practical difficulties there may be in the way of the successful employment of antitoxic serum in the treatment of human diphtheria, but there is no doubt in my mind that the results derived from experiments on animals justify, nay, demand, the most careful and thorough trial of the new method of treatment upon human beings.

We have no certain knowledge as to the nature of the substances called antitoxins nor as to their mode of action. This is not, however, an argument against their therapeutic employment, for we have no positive knowledge as to the mode of action of many of our therapeutic agents. There are two prominent theories as to the mode of action of the diphtheria antitoxin. The one may be called the chemical and the other the vital theory. The chemical theory is that the antitoxin directly neutralizes in a chemical sense the toxins. This seemed to be the natural interpretation of the fact that the injection into susceptible animals of a mixture in suitable proportion of the antitoxin and the toxin is harmless, but Buchner and Roux have shown that this earlier view is incorrect, and that by selecting animals of greater susceptibility or by increasing the natural susceptibility of an animal, the presence of active toxin in the mixture can still be demonstrated. The experimental evidence, therefore, is in favor of the other theory, viz. that the antitoxin acts through the agency of the living body, and probably in the sense that it renders the cells tolerant of the toxin.

The results of the treatment of human diphtheria with antitoxin speak also in favor of this vital theory.

If, as seems probable, the curative effects of the healing serum are brought about through the agency of the living cells of the body, we can understand why these effects will not follow the introduction of the serum with the certainty and precision of a chemical reaction. The cells must be in a condition to respond in the proper way to the introduction of the antitoxic serum. For one reason or another this responsive power may be in abeyance. It may be weakened by intense or prolonged action of the diphtheria poisons, or by other previous or coexistent disease, or by inherent weakness, or there may even be some individual idiosyncrasy which hinders the customary response of the cells to the antitoxin. Clinical experience shows that cases of diphtheria inherently refractory to timely treatment with antitoxic serum are most exceptional, if indeed they occur at all.

There is some evidence in favor of the view that while antitoxin may exert its protective action upon certain groups of cells, other cells, as for example the nerve cells, may, either by their nature or on account of such influences as I have mentioned, not be equally protected against the toxin. There is also the possibility that antitoxin may neutralize the effects of certain toxins and not of others present in diphtheria.

Antitoxic serum exerts no bactericidal effect upon the diphtheria bacillus, although, when administered in proper quantity, sufficiently early in the disease, it arrests the spread of the local inflammation which is caused by the bacillus. Virulent bacilli may persist in the throat days and even weeks after recovery following injection of antitoxin.

One of the most important characters of antitoxin is that it requires a definite quantity of this substance to neutralize the effects of a definite quantity of toxin. In animals the curative dose of antitoxin stands in a definite quantitative relation to the size and susceptibility of the individual and to the amount and intensity of the poison in the system. We have no precise method of determining how much and how virulent the poison may be in a given case of human diphtheria nor how susceptible to the toxin the patient may be. The dosage

of antitoxin, therefore, in human diphtheria is empirical, the main factors determining it being the age of the patient, the assumed duration of the disease up to the time of administering the remedy, and the apparent severity of the disease. As the healing serum is expensive and is capable of inducing unpleasant symptoms, it is desirable not to give an excessive quantity. Under these circumstances it may readily happen that an insufficient dose is given and that the administration must be repeated. The general rules regarding the dosage of antitoxin are sufficiently well known not to require mention here, and I speak of this matter only to indicate that because a patient may have received a dose or even two or more doses of antitoxin, this furnishes no absolute guarantee that a quantity of antitoxin adequate to neutralize the effects of the toxin has been given. We now know that in the early period following introduction of the treatment entirely insufficient doses were given.

Both experiments on animals and clinical experience demonstrate that the earlier antitoxic serum is administered after the inception of the disease, the better are the chances of recovery. It is usually impossible to rescue the lives of guinea-pigs by means of antitoxin if the treatment is delayed longer than forty-eight hours after inoculation with an amount of diphtheria poison fatal to these animals in four or five days, although the duration of life may be considerably prolonged. In human beings the conditions are different, but, as will appear from the statistics to be presented, the evidence is conclusive that the superiority of serum treatment over all other methods is most strikingly manifested in the results of the cases in which the antitoxin is given not later than the third day of the disease. Although in many cases the treatment is beneficial when the antitoxin is administered in larger doses at a later period of the disease, the importance of beginning the treatment at the earliest possible date, without waiting to determine by cultures whether or not the Löffler bacillus is present, cannot be too strongly emphasized.

It is of course often impossible to meet this demand for early treatment, as cases of diphtheria are frequently not seen or recognized by the physician, particularly in hospital practice, until after several days' duration of the disease and when grave symptoms have already developed. It is, moreover, in many cases difficult or impossible to determine how long the disease has existed when it is first seen by the physician.

The fact that the benefits of antitoxin treatment become more and more doubtful the further the disease has progressed and the graver the lesions and symptoms, renders more difficult the collection and analysis of absolutely convincing statistics in favor of the treatment. The accusation is sure to be brought that many of the cases which have responded promptly to early treatment, and these for reasons which have been stated will form a large contingent of the successful cases, were mild cases which would have recovered equally by other methods of treatment. This objection can be fully met only by large series of statistics collected from many epidemics, at different times and in various localities.

The bacteriological study of human diphtheria has disclosed several points important to bear in mind in determining the value of antitoxic treatment. The Löffler bacillus has been found in healthy throats, although only very exceptionally unless the person has been exposed to diphtheria. This same bacillus may cause all grades of inflammation of the throat, from a mild erythematous angina to the gravest pseudo-membranous inflammations. There has resulted a conflict, not yet settled, between the clinical and the bacteriological diagnosis of diphtheria. As regards these diversities of effect, however, the conditions pertaining to the diphtheria bacillus are in no way different from those relating to many other pathogenic bacteria, as for example the pneumococcus, the streptococcus, the cholera bacillus, and even the tubercle bacillus, all of which may be found on healthy mucous membranes and may exert their pathogenic activity with all degrees of intensity. Inconvenient as these facts may be, they must be recognized, and they require a readjustment of previously adopted boundary lines of diagnosis. It would, of course, be absurd to say that a person who harbors in his healthy throat Löffler bacilli has diphtheria, just as it would be equally ridiculous to consider a person infected with the pneumococcus or the streptococcus when these latter bacteria are present under similar conditions, but it is no less absurd to limit the application of the term "diphtheria" only to those higher degrees of pathogenic action of the Löffler bacillus characterized by spreading pseudo-membranous inflammations and general toxæmia.

But while the boundaries of the domain of diphtheria have thus been widened by the inclusion of cases not presenting the ordinary clinical characteristics of diphtheria, in another direction they have been restricted by the exclusion of some cases which on clinical grounds would be diagnosed as diphtheria but which by bacteriological examination are proven to be caused by other bacteria than the Löffler bacillus.

The statement is sometimes made that twenty-five to thirty per cent., or even a larger percentage of the clinical diphtherias are not genuine diphtheria in the bacteriological sense, but this statement is quite misleading. These figures are based upon the bacteriological examination of large numbers of cases in which there was simply more or less suspicion of diphtheria. They do not relate generally to a large number of cases presenting unmistakable anatomical and clinical characteristics of diphtheria. They are derived from the routine examinations for Boards of Health and children's hospitals of suspected cases of diphtheria. When one considers that in some cases of diphtheria repeated, painstaking examination, microscopical and cultural, by a skilled bacteriologist, is required for the detection of the diphtheria bacillus, it is evident that less reliance is to be placed upon these statistics *en gros* than upon many smaller series reported by bacteriological experts. Of the statistics of the latter character there are many which show that in the series of cases examined (including in each series from a dozen to over three hundred cases) from ninety to one hundred per cent. of the clinical diphtherias are due to the Löffler bacillus. Our experience in Baltimore has been that not over five per cent. of the cases which the clinician would confidently diagnose as diphtheria are false diphtheria or diphtheroid. These latter figures relate, of course, to primary diphtheria and not to the pseudo-membranous anginas complicating scarlet fever and

other infectious diseases, a large proportion of which are not referable to the Löffler bacillus.

I shall consider subsequently in this article the influence which the control of the clinical diagnosis of diphtheria by bacteriological examination is likely to have upon fatality statistics of this disease.

There is an important difference between experimental diphtheria and many cases of human diphtheria, a difference of great significance in determining the scope of efficiency of treatment by antitoxic serum. Our experimental diphtheria is a pure, uncomplicated infection in which only the diphtheria bacillus and its toxins are concerned. On the other hand, in many cases of human diphtheria there are complications and mixed infections due to other micro-organisms against which, when duly developed, the diphtheria antitoxin is powerless. The most common and dangerous complicating micro-organism is the streptococcus pyogenes. Bacteriological examinations of fatal cases of diphtheria demonstrate in a large proportion of cases the invasion and pathogenic effects of this most common of all secondary invaders. The confidence with which some observers, particularly of the French school, classify their cases of diphtheria into pure and mixed infections, on the sole basis of the bacteriological examination of the exudate in the throat, does not seem to me justifiable. The complete microscopical and cultural examination of this exudate will in practically all cases reveal the presence of other bacteria, and usually of streptococci, besides the Löffler bacillus. But as these other bacteria are common or regular inhabitants of the healthy throat, their mere presence in this situation is not conclusive evidence that they are engaged in pathogenic action. The abundance of these other bacteria may afford some indication as to their rôle, but of greater importance is their demonstration in situations where they are not normally present.

Reiche,* in 42 autopsies on cases of diphtheria in which the Löffler bacillus had been demonstrated during life, made cultures from the kidney and spleen. In 64.3 per cent. of these cases streptococci and staphylococci were found in the kidney or spleen, and in 45.2 per cent. streptococci were found alone. These cocci must have reached these organs through the circulating blood. He found streptococci in the kidney in one case which died on the second day of the disease, and positive results were obtained also on the third and fourth day. These results are evidently of much significance in indicating the frequency and the earliness of invasion of complicating micro-organisms in diphtheria and the resulting obstacles to uniformly favorable results of antitoxin treatment.

But the chief evidence in favor of mixed infection must be sought during life, in the character of the lesions and symptoms, although these may be misleading. There is also evidence that the failure of a case of diphtheria to respond in the usual way to the timely injection of a sufficient dose of antitoxic serum is an indication of complications and mixed infection.

The opinion is entertained by Roux, Martin and other French writers that broncho-pneumonia, one of the most common and serious complications of diphtheria, is due to a large extent to local unhygienic conditions which can be guarded against. Thus they attribute the frequent occurrence of broncho-pneumonia in some groups of their cases to the infection of the hospital wards with the bacteria causing pneumonia, and claim that by improved sanitary conditions this complication may be to a large extent eliminated. Further investigations are needed to determine to what extent this view as to the causation of broncho-pneumonia is justified, but it can scarcely be doubted that this complication is often the result of invasion of the lower air passages and the lungs by bacteria which are regularly present in the throat, and whose activity is likely to be manifested in this way in many cases of diphtheria, independently of the local sanitary conditions.

Without doubt the remedial rôle of diphtheria antitoxin is materially restricted by its inability to combat developed streptococcus sepsis, broncho-pneumonia and other complications referable to secondary infection, or to stop impending suffocation by immediate removal of mechanical obstacles in the form of false membranes in the air passages, but the antitoxic serum is the most powerful agent which we possess to prevent the development of these complications and secondary infections. The timely administration of the healing serum, by antagonizing the effects of the Löffler bacillus, antagonizes in large part the causes of the increased susceptibility to secondary infections and thus greatly lessens the frequency of their occurrence.

In considering the obstacles in the way of cure of diphtheria by antitoxin, the self-evident fact should not be forgotten that this remedy cannot restore cell life which has already been seriously damaged by the action of the diphtheria bacillus or its poison. The researches of Oertel upon human diphtheria, and those of Flexner and myself upon experimental diphtheria, demonstrate that the toxins of the diphtheria bacillus are most powerful poisoners of cells, the internal lesions of pure diphtheria being especially characterized by widely distributed areas of cell death. We have no way of gauging accurately at any given period of the disease the extent of the damage already inflicted upon the cells of the body. If the nerve cells or their axis cylinders have already been so damaged that paralysis must follow, or the cardiac nerve cells or muscular fibres have been similarly injured, or the renal epithelium so affected that degeneration and nephritis ensue, the administration of antitoxin cannot restore these cells which are already on the way to degeneration and death.

This irretrievable damage to cell life may be present for a considerable time before we are able to recognize its effects. P. Meyer detected pathological changes in the peripheral nerves as early as the third day after the onset of diphtheria and before paralysis was manifest. The occurrence of paralyses, including cardiac paralysis, after antitoxin has been administered even thus early in the disease, cannot therefore necessarily be attributed to failure of this agent to neutralize toxin developed after its injection.

Having now considered the experimental basis and the

*Reiche: Centralblatt f. innere Medicin, 1895, No. 3.

theories of action of antitoxic treatment, the importance of early administration and sufficient dosage, and certain etiological and pathological characters of human diphtheria to be borne in mind in estimating the scope of the treatment, let us turn to the examination of the evidence which has hitherto been published concerning the efficacy of the antitoxic treatment of human diphtheria. This evidence is of two kinds, first, the general impressions of clinicians who have had opportunity to observe the effects of antitoxin administered in a number of cases of diphtheria, and second, the fatality statistics of cases treated with antitoxin.

Unquestionably great value attaches to the impressions and conclusions of careful clinical observers as to the merits of therapeutic agents. Baginsky has said that naked figures are so little the expression of the endless variations of clinical observation, of all those fortunate and unfortunate accidental circumstances which pertain to the constitution and nutrition of the patient, and of the complications and difficulties which may bring danger in a mild attack, or lead to a successful issue an apparently severe attack, that to the clinical observer such figures appear of little value in comparison with the treasure-house of his accumulated experience. And it is to his experience of many years in the same hospital and on similar clinical material that Baginsky repeatedly recurs in his monograph "Die Serum-therapie der Diphtherie," in support of his favorable conclusions as to the healing power of antitoxin, and this in spite of the fact that his statistical results, leading to the same conclusions, are based upon a larger number of cases than those of any other single observer yet published, and are among the most convincing of the statistical reports. In explaining why at the end of ten months' trial of antitoxin he has determined to commit himself to a definite judgment in its favor, he says: "The reasons for this are to be found in the continual repetition of improvement and recovery of severe cases which previous experience indicates would have terminated fatally; and furthermore, in the outcome of an involuntary experiment with interruption of the use of the serum for a period on account of failure in its supply. During this period the mortality of our patients immediately rose again to its former height." "The improvement in the general condition of the patients imparts to our diphtheria wards an entirely different character from the former one. That this is not due to any change in the character of the clinical material, to milder forms of the disease, was unfortunately demonstrated by the observations in the months of August and September, when, as by a single blow, we were transported back to the old times, to the same melancholy picture of children deeply prostrated and often in vain struggle with death." In August and September the supply of antitoxin failed.

The published testimony of those who have had the largest opportunity to study the therapeutic effects of antitoxin is overwhelmingly in its favor. In no less favorable terms than those of Baginsky are expressed the opinions of such observers of high reputation and extended experience as Heubner, von Widerhofer, von Ranke, Ganghofner, Escherich, Bokai and the physicians of the Hôpital des Enfants Malades and Hôpital Trousseau in Paris. These observers have reported already in detail over 2300 cases of diphtheria treated with antitoxin.

Many of those who have reported smaller series of cases, and a few who have reported as many as a hundred cases, have expressed themselves with much caution or have not ventured any final judgment, although in most of these reports the results appeared to be favorable to the new treatment. An example of this conservative position is that of Vierordt, who says that a final decision as to the value of antitoxic serum is not to be expected in the immediate future, as such decision requires a long series of observations in different epidemics and on varied clinical material.

Antitoxic serum is a new and strange remedy, but the effects which follow its injection in individual cases are not new and strange. Nothing happens which the physician may not have occasionally seen to happen in cases treated in the ordinary way. In severe as well as in mild cases of diphtheria he may have seen an apparently progressive local process quickly arrested and the general symptoms promptly abated. But why should anything new and strange happen after the administration of antitoxin? Cure by antitoxin is cure by nature's own remedial agent. That which is new and strange is the frequency with which in case after case the timely injection of antitoxin promptly arrests the local inflammation and checks the constitutional disturbance.

Recovery following treatment by antitoxin is such a natural kind of recovery that in any given case the physician may readily have the feeling that the same thing might have happened without the use of the remedy. We can, therefore, understand why it should be those with the largest experience in the treatment of diphtheria by antitoxin who are most decided in expressing their opinion as to its beneficial effects. The very fact that the mode of cure is such a natural one and unattended by peculiar phenomena is an obstacle to drawing positive conclusions from a small number of observations, even if these appear to be most favorable.

That there should be wide diversity in the percentage of cures in reports of different observers is of course to be expected when we consider the varied character of the cases treated and the importance of early administration of antitoxin. It may happen that a series of cases is made up so largely of advanced and complicated diphtherias at the time when the antitoxic treatment is begun, that the beneficial effects of the treatment are not apparent. It is on the whole remarkable that there should have been so few reports in which the fatality has not been materially diminished during the period of administration of antitoxin.

There are only very few writers who on the basis of personal experience (and this in no instance a large one) have expressed an opinion unfavorable to antitoxin. Kohts may be mentioned as one who on the basis of 47 cases treated with serum, with 29.1 per cent. deaths among the tracheotomized and 7.6 per cent. among the non-tracheotomized, finds such apparently favorable results no better than by other methods of treatment.

So far then as the testimony of physicians based upon their clinical experience is concerned, this, as I have already said, is overwhelmingly in favor of the antitoxic treatment, wherever

their experience in its employment has been a large one. Those with less experience are often even more enthusiastic, but many of these, in view of their limited experience, are wisely conservative and a few are hostile to the new treatment.

But general clinical impressions, convincing as they may be to the individual receiving them, may not be equally convincing to others. They do not furnish any strict scientific proof of the value of a therapeutic agent. If antitoxin really exerts any specific curative action in diphtheria this must be apparent in the figures of fatality statistics of this disease, and it is only by such statistics, much as they may be decried by some, and difficult as it may be to guard them from errors of interpretation, that a strictly scientific demonstration of the efficacy of antitoxin in the treatment of diphtheria can be brought.

The possible fallacies of interpretation belonging to fatality statistics in general apply in no small measure to those of diphtheria. The case mortality from diphtheria varies within wide limits according to the more or less severe character of the prevailing epidemic, according to the season of the year, according to the age, according to the method of treatment, in cities and in country districts, etc. Statistics of case mortality from hospital practice will differ widely from those from private practice, and each of these will differ from the general case mortality returns from cities. Nor does each of these three classes of statistics represent a uniform material. The material of one hospital may consist very largely of cases of diphtheria admitted in an advanced stage of the disease, or of laryngeal cases sent for operation, while that of another hospital may contain a much larger proportion of cases admitted in early stages of the disease. In general the fatality of diphtheria in hospital practice is higher than that of private practice, as would be expected from the later stage of the disease in which the patients generally enter the hospital; but to this rule there are many exceptions. In some hospitals the patients are all children, in others there may be a considerable proportion of adults with diphtheria. In private practice among the poor, patients may be first seen by the physician frequently in as advanced stages of the disease as in hospitals, and the conditions for successful treatment, and particularly for intubation or tracheotomy, are less favorable for this class of private patients than for hospital patients.

Still other reasons might be given for the lack of uniformity of diphtheria statistics from different sources, but enough has been said to show that as regards the question which interests us here, each report of a series of cases treated with antitoxin requires its own special consideration and analysis and is not comparable with reports from other sources relating to a different class of cases.

The larger the number of cases embraced in the statistical tables, the greater becomes the mutual compensation of such differences as those mentioned, and therefore the more trustworthy are the conclusions derived from the statistics; but in collecting the statistics of the general fatality of diphtheria treated with antitoxin it has seemed to me important, for the reasons which have been mentioned, that the tables should contain for each report, as far as possible, statements of the total number of cases treated with antitoxin, of the number and percentage of deaths, of the previous or simultaneous fatality, and of the class of cases, whether in hospital or in private practice. I have also analyzed the cases so far as practicable according to the ages of the patients and according to the day of the disease on which antitoxin treatment was begun. It has seemed to me of especial interest to consider the fatality in operated and not operated cases. There are of course many other points of view which it would have been interesting to consider in the statistical study of the cases reported, but it has seemed to me that the analysis already indicated should suffice to determine the main question at issue, namely, the specific curative power of antitoxin, as well as certain other questions.

It is scarcely ten months since antitoxin has been used by more than a very few favored physicians, and it is a much shorter time since its use has become at all general. In this comparatively short time there have, however, been published more or less definite reports of the results of the treatment in at least 15,000 cases. I have collected 82 reports from 80 different sources containing 7166 cases. These are presented in Table I. This collection of cases is by no means complete, as I have consulted only the more readily accessible journals, but it is believed to include all of the more important reports. I have not included any reports of single cases, as these are often to illustrate some special point, nor any reports of series of cases less than ten. Indeed only four reports with less than 12 cases in the group have been included in the tables. Nor have I made use of such merely general published statements without detail as that there have been treated in France up to the end of December 2700 cases with a mortality of 16 per cent., in Austria outside of Vienna 950 cases with a mortality of 15.7 per cent., in Croatia and Slavonia 428 cases with a mortality of 10.8 per cent., in Berlin hospitals 1500 cases with a reduction in fatality of one-half, etc.

Eulenberg has recently (July 15, 1895) made a provisional report concerning the collective investigation inaugurated by the Deutsche medicinische Wochenschrift by sending out cards to be filled out by physicians regarding their results in the treatment of diphtheria with and without serum. Up to the date of the report the cards returned embraced 10,240 cases of diphtheria, of which 5790 were treated with serum and 4450 without serum. The total fatality of the former group was 9.5 per cent., that of the latter group 14.7 per cent. No further details of this investigation have as yet been published, and these cases are not included in my tables.

I have entirely avoided the duplication of cases, so far as I can determine.* There has been no selection whatever of cases. All of the reports of the characters described which came to my notice are included, although many of the early

*This duplication of cases appears in several of the published statistics, especially of the Berlin statistics. Thus the cases reported by Schubert, Voswinckel, Canon and Weibgen appear in the report of Ehrlich, Kossel and Wassermann, and partly in the reports of Körte, Sonnenburg and Hahn, sometimes twice repeated. Most of these cases are included without duplication, in my table, although they were treated with insufficient doses to a large extent. The cases attributed to Virchow, Aronson and Katz in some statistics are included in those of Baginsky.

Berlin cases (contained in statistics of Körte, Sonnenburg and Hahn in my tables) and some of the others were treated with entirely insufficient doses of antitoxin, and some observers have purposely selected, especially at the time when little serum was to be had, only severe cases for treatment. Kohts' 47 cases could not be inserted, as in the report which I have seen he does not give the number of deaths.

The reports are of unequal value. Some present full and precise details of each case or of the group of cases, with statements as to previous or simultaneous fatality in the same class of cases in the same locality, whereas others are meagre and unsatisfactory.

Some reports are based upon the bacteriological control of the clinical diagnosis, others upon the clinical diagnosis uncontrolled by bacteriological examination. In general the statistics from the larger hospitals relate to cases in which the Löffler bacillus was demonstrated, whereas many of the reports from private practice are without bacteriological examination. A few, notably Leichtenstern and Wendelstadt, purposely base their observations upon cases in which the diagnosis is purely clinical without bacteriological control.

I shall take this opportunity to consider the influence which the requirement of the bacteriologist, that the clinical diagnosis of diphtheria should be controlled by a bacteriological examination in testing the efficacy of antitoxin treatment, is calculated to have upon the characters of statistics intended to show the value of the treatment. It is a favorite criticism of these statistics that the bacteriological, as distinguished from the purely clinical, diagnosis of diphtheria will operate in favor of a low fatality in antitoxin statistics, and that therefore it is unfair to compare these statistics, with those which are based upon the uncontrolled clinical diagnosis of diphtheria. Some of the critics would have us believe that the antitoxin statistics on the one hand contain a large proportion of cases of mild inflammation of the throat with Löffler bacilli, but which no clinician would recognize as diphtheria, and on the other hand exclude a large proportion of fatal pseudo-membranous inflammations of the throat and air passages which clinically would be regarded as diphtheria.

In most of the statistical reports from hospitals on antitoxin treatment the statement is expressly made, and it is apparent from the description of the cases, that they do not represent anything else than the usual run of cases of diphtheria as they have regularly for years past presented themselves at the same hospitals. The mild diphtheric sore throats without clinical evidences of ordinary diphtheria are not likely in any large number to be recognized at all as diphtheria, and still less likely to find their way into general hospitals, from which most of the statistics are derived. Where, as in the statistics of Baginsky and others, sufficient detail concerning each case is reported to enable the reader to form an intelligent estimate of the character and severity of the case, it is evident that affections without the customary anatomical and clinical characters of diphtheria do not enter into the statistics.

It is erroneous to say that the antitoxin statistics are not based upon the clinical diagnosis of diphtheria. The diagnosis is clinical, but with subsequent bacteriological control. The cases are admitted to the hospital with the clinical diagnosis of diphtheria, and the healing serum is or should be at once administered without waiting for the result of the cultures from the throat. Soltmann has been justly criticised for delaying the injection of antitoxin until after the bacteriological examination was completed.

The assumption that non-membranous anginas and tonsillitis containing Löffler bacilli figure to any appreciable extent in these statistics is without warrant of facts.

There are treated of course together with severe cases many mild cases with small patches of membrane on the tonsils or in the throat, but such cases are clinically diphtheria, or certainly ought to be suspected of diphtheria by the clinician. It is important that such cases, when caused by the Löffler bacillus, especially in young children, should be treated by antitoxin, for not a few such cases when untreated develop into severe cases, sometimes suddenly into laryngeal diphtheria. Kurth, for example, relates a case in which a twin brother of a child ill with diphtheria was found to present small membranous patches on the tonsils which during two weeks of observation would at times disappear and which did not apparently make the child ill. Löffler bacilli were demonstrated, but the parents would not consent to the injection of serum. At the end of fourteen days, laryngeal diphtheria suddenly developed. The injection of antitoxin was followed by recovery in four days. This is simply a type of not a few cases which are regarded as suddenly developed laryngeal diphtheria.

If, as is doubtless true, in some hospitals a larger number of cases are now received for serum treatment in earlier stages of diphtheria than formerly, this is not because the bacteriological diagnosis has supplanted the clinical, but because the importance of early inception of serum treatment has been justly emphasized. The recognition of mild and very mild cases of diphtheria is not a discovery of the bacteriologist, but has long been known to physicians, nor is it a peculiarity of the fatality statistics of cases treated by antitoxin that such mild cases are included in the statistics. They appear equally in previous fatality statistics of diphtheria. Mosler, for example, reports 313 cases of diphtheria with a fatality of 14.5 per cent. treated during a year in the Greifswald clinic before the introduction of serum, and there are numerous other statistics showing that mild cases often preponderate in previous fatality statistics of diphtheria. Nor is the comparison in all of the reports with statistics in which the diagnosis is without bacteriological control. In several reports the comparison is with the results of cases in which the Löffler bacillus was demonstrated, but which were not treated with serum.

As regards the exclusion from antitoxin statistics of cases presenting the clinical characters of diphtheria without the Löffler bacillus, it is evident, from what has previously been said, that, with thorough bacteriological tests, this can affect only a very small number of cases of unmistakable primary clinical diphtheria. Of the cases concerning which the clinician is in doubt, a considerable proportion are not diphtheria by bacteriological examination, which alone can decide the question. Although some of the non-diphtheric, pseudo-membranous cases are very grave affections, their general

fatality is much lower than that of genuine diphtheria. The exclusion from the fatality statistics of diphtheria of the pseudo-membranous cases without Löffler bacilli is, therefore, the exclusion of a generally milder class of cases, as has been repeatedly demonstrated, and the result is to assign a higher and not a lower fatality to the remaining cases. A few examples taken from reports in Table I will suffice to demonstrate this. From the statistics of Roux, Martin and Chaillou 128 pseudo-membranous cases treated with serum were thrown out because they were proven subsequently to be devoid of Löffler bacilli. The fatality of these cases was only 8.5 per cent., whereas in the 300 remaining cases which contained Löffler bacilli and were injected with serum the fatality was 26 per cent. In Sevestre and Meslay's statistics 29 cases without Löffler bacilli, but treated with serum, gave a fatality of 3.4 per cent. as opposed to a fatality of 10 per cent. in the treated cases containing Löffler bacilli. A similar difference appears in other reports. The serum has no curative influence on pseudo-membranous inflammations not caused by the Löffler bacillus.

In the best reported statistics information is afforded as to these various points, and the reader can learn the ratio of apparently mild cases and the number and results of the diphtheroid cases.

Although only those statistics which are based upon the thorough bacteriological examination of the cases treated can lay claim to entire accuracy, the benefits of antitoxic treatment are clearly apparent in reports based upon the uncontrolled clinical diagnosis of diphtheria. Of course in ordinary general practice it is not to be expected that the diagnosis will rest upon a bacteriological examination, but it should be understood that in the absence of such examination there must be occasional instances of apparent failure of antitoxin which would be found explicable had a bacteriological examination been made.

In many reports the percentage of deaths in the cases treated with antitoxin is corrected by excluding cases evidently hopeless on admission or dying within twenty-four hours after commencement of the treatment. These corrected percentages are usually very materially lower than the rates based on all of the deaths. For example, if the cases dying within twenty-four hours after injection of antitoxin be excluded, the percentage of deaths in Roux, Martin and Chaillou's cases becomes 21.5 instead of 26; in Baginsky's 13.5 instead of 15.6; in von Widerhofer's 14.3 instead of 23.7; in Vierordt's 14.6 instead of 25; in Lebreton and Magdelaine's 10.8 instead of 12; in Moizard and Perregaux's 11.3 instead of 14.7; in Sevestre and Meslay's 6.6 instead of 10; in Bokai's 18.3 instead of 25.5, etc. I have, however, not used these reduced percentages, although in many instances it might with propriety have been done. The statistics in my tables, therefore, do not give in many instances as favorable percentages for antitoxin as may justly be claimed, but on the other hand they are more properly comparable with the previous or simultaneous fatality rates from diphtheria, these being based upon the total number of deaths in all of the cases treated. I have aimed to avoid the accusation of selection of cases or of unfair manipulation of the figures.

In the majority of the reports the cases treated are all or nearly all of the cases of diphtheria which were admitted to the hospital or came under observation during the period of treatment, but in some it is expressly stated that in consequence of the cost and the scarcity of the healing serum mild cases and evidently hopeless cases did not receive the serum. There is no evidence of selection of mild cases in order to obtain results favorable to antitoxin.

The percentages in the column headed "Previous Fatality" are those given by the writers for diphtheria not treated with antitoxin. In some instances they relate to the average fatality for a series of preceding years, in some to the minimum and the maximum fatality for several years, in some to the simultaneous fatality or the fatality during a period of interruption in the supply of serum. In all instances they are the case mortality rates of diphtheria in the hospital or locality from which the cases treated with antitoxin are derived. The arrangement of the reports is only in part chronological. Following the references to the articles, it is stated, so far as could be ascertained, whether the cases were in hospital or in private practice.

It appears from Table I* that of 7166 patients with diphtheria treated with antitoxin 1239 or 17.3 per cent. died. Among these cases are included many treated during the early period after the first introduction of the treatment, with entirely insufficient doses. There are also included a large number of cases dying from complicating diseases not referable to diphtheria, or dying within twenty-four hours after beginning the treatment, cases which cannot properly be regarded as indicating failure of the serum treatment. The great bulk of the statistics come from children's hospitals. Under these circumstances, indeed from any point of view, the fatality derived from Table I of cases treated with antitoxin is very low.

There is, however, no standard of comparison for the fatality in this entire group of cases. It cannot be compared with fatality statistics from hospitals nor with those from private practice. The table contains at least five or six times as many cases from hospital practice as from private practice. The ratio of deaths to all cases, therefore, is greater than could be expected from the returns of all cases similarly treated in cities, but even in comparison with municipal fatality statistics of diphtheria during the prevalence of mild types of the disease, the percentage of deaths is very low. This strikingly low fatality in itself speaks strongly in favor of the efficacy of the serum treatment.

In 46 reports contained in the table the previous or simul-

*The report of Fürth concerning the results of serum treatment in the medical and surgical clinics at Freiburg was published too late to be included in my tables. 100 cases were treated with a fatality of 12 per cent. During the five preceding years the fatality from ordinary treatment fluctuated between 31 and 49 per cent., averaging 39 per cent. The same average existed during the seven months of the year corresponding to the period during which antitoxin was used. There was laryngeal involvement in 43 cases and tracheotomy was performed in 31 with 11 deaths (35.4 per cent.). In previous years tracheotomy was required in 46.2 per cent. of the cases, with a mortality of 70.4 per cent. (Abstract in the Medical News, August 17, 1895.)

TABLE I.—FATALITY OF CASES OF DIPHTHERIA TREATED WITH ANTITOXIN.

NUMBER OF CASES TREATED WITH ANTITOXIN, THE NUMBER AND PERCENTAGE OF DEATHS, AND THE PREVIOUS FATALITY, IN 82 REPORTS.

REPORTER.	CASES.	DEATHS.	PREVIOUS FATALITY.	REFERENCES.
1. Roux, Martin and Chaillou.	300	78 (26 per cent.)	50 per cent.	Annales de l'Institut Pasteur, Sept., 1894. (Cases in Hôpital des Enfants-Malades.)
2. Kossel.	117	13 (11.1 per cent.)	52–61 per cent.	Deutsche Med. Wochenschrift, 1894, p. 946. (Hospital.)
3. Körte.	121	40 (33.1 per cent.)	45.1 per cent.	Berliner Klin. Wochenschrift, 1894, p. 1039. (Hospital.)
4. Sonnenburg.	95	16 (16.8 per cent.)	27.6 per cent During period of interruption of serum treatment.	Deutsche Med. Wochenschrift, 1894, p. 930. (Hospital.)
5. Hahn.	205	49 (24 per cent.)	41 per cent.	Ibid. 1895, Vereins-Beilage, p. 2. (Hospital.)
6. Baginsky.	525	83 (15.6 per cent.)	41 per cent.	Die Serumtherapie der Diphtherie. Von Dr. Adolf Baginsky, Berlin, 1895. (Hospital.)
7. Heubner.	207	27 (13 per cent.)	48-52 per cent.	Reported at 13ter Congress für Innere Medicin, München, April 2, 1895. Münchener Med. Wochenschrift, April 9, 1895. (Hospital.)
8. v. Widerhofer.	300	71 (23.7 per cent.)	50 per cent.	Ibid. (Hospital.)
9. v. Ranke.	96	19 (19.7 per cent.)	42.2–56 per cent.	Ibid. (Hospital.)
10. Stintzing.	59	12 (20.1 per cent.)	25 per cent.	Ibid. (Hospital.)
11. Rauchfuss.	100	34 (34 per cent.)	55 per cent.	Ibid. (Hospital.)
12. v. Mering.	74	4 (5 per cent.)	30 per cent.	Ibid.
13. v. Noorden.	81	19 (23 per cent.)	45 per cent.	Ibid. (Hospital.)
14. Schröder.	63	8 (12.7 per cent.)	30-37 per cent.	Ibid. (Hospital.)
15. Vierordt.	63	16 (25 per cent.)	41-67 per cent.	Deutsche Med. Wochenschrift, 1895, p. 160. (Hospital.)
16. Rumpf.	22	2 (8 per cent.)	13–28 per cent.	Münchener Med. Wochenschrift, Nov. 20, 1894. (Hospital.)
17. Lebreton and Magdelaine.	258	31 (12 per cent.)	50 per cent.	Le Bulletin Médical, 1895, No. 10. (Hôpital des Enfants-Malades.)
18. Le Gendre.	17	3 (17.6 per cent.)	50-60 per cent.	Bull. et Mémoires de la Soc. Méd. des Hôpitaux de Paris, Dec. 20, 1894, (Hôpital Trousseau.)
19. Moizard and Perreganx.	231	34 (14.7 per cent.)	50–60 per cent.	Jour. de Médecine et de Chirurgie, Dec. 15, 1894. (Hôpital Trousseau.)
20. Sevestre and Meslay.	150	15 (10 per cent.)	50–60 per cent.	Le Bulletin Médical, 1895, No. 18. (Hôpital Trousseau.)
21. Ganghofner.	110	14 (12.7 per cent.)	43.6–78.2 per cent.	Prager Med. Wochenschrift, 1895, Nos. 1, 2 and 3. (Hospital.)
22. Soltman.	89	13 (14.6 per cent.)	27.2 per cent.	Deutsche Med. Wochenschrift, 1895, No. 4. (Hospital.)
23. Bokai.	176	42 (24 per cent.)	53.5–67.5 per cent.	Ibid. 1895, No. 15, and Wiener Med. Presse, 1895, No. 12. (Hospital.)
24. Escherich.	51	5 (9.5 per cent.)	.....	Abstract in Münchener Med. Wochenschrift, 1895, No. 7. (Hospital.)
25. Gnändinger.	27	11 (40.7 per cent.)	36–45.5 per cent.	Wiener Klin. Wochenschrift, 1895, No. 1.
26. Monti.	25	1 (4 per cent.)	...	Wiener Med. Wochenschrift, 1895, Nos. 4 and 5. (Hospital.)
27. Heim.	27	6 (22 per cent.)	52.5 per cent.	Ibid. 1895, No. 4. (Hospital.)
28. Unterholzner.	31	8 (25.8 per cent.)	66.7 per cent.	Ibid. (Hospital.)
29. Bäumler.	26	2 (7.7 per cent.)	...	Münchener Med. Wochenschrift, 1894, p. 1002. (Hospital.)
30. Börger.	30	2 (6.66 per cent.)	20 per cent.	Deutsche Med. Wochenschrift, 1894, No. 48. (Hospital.)
31. Hilbert.	11	0	....	Ibid. 1894. Vereins-Beilage, p. 142. (Hospital.)
32. Hager.	25	1 (4 per cent.)	....	Centralbl. f. innere Medicin, 1894, No. 48. (Private practice.)
33. Moeller.	76	27 (35.5 per cent.)	....	Ibid. (Hospital.)
34. Kuntzen.	25	3 (12 per cent.)	....	Deutsche Med. Wochenschrift, 1894. No. 49. (Hospital.)
35. Schmidt.	14	3 (21.4 per cent.)	....	Deutsche Med. Wochenschrift, 1894, No. 52. (Private practice.)
36. Seiz.	27	1 (3.6 per cent.)	30.6 per cent.	Therapeut. Monatshefte, Dec., 1894. (Private practice.)
37. Charon.	13	4 (30.8 per cent.)	....	Annales de la Soc. Royale des Sciences Médicales et Naturelles de Bruxelles, T. III, p. 337 (1894). (Hospital.)
38. Washbourn, Goodall and Card.	72	14 (19.4 per cent.)	36–41.8 per cent.	Brit. Med. Jour., Dec. 22, 1894. (Hospital.)
39. Seitz.	35	2 (5.7 per cent.)	....	Abst. in Münchener Med. Wochenschrift, 1895, No. 12. (Hospital.)
40. Pavlik.	13	1 (7.7 per cent.)	....	Wiener Med. Presse, 1895, Nos. 1 and 5. (Private practice.)
41. Handler.	32	5 (15.6 per cent.)	..	Ibid. No. 6. (Private practice.)
42. Herringham.	18	3 (16.7 per cent.)	....	Brit. Med. Journ., Dec. 22, 1894. (Hospital.)
43. Caiger.	30	8 (26.6 per cent.)	30 per cent.	Ibid. Dec. 29, 1894. (Hospital.)
44. Hall.	11	3 (27.3 per cent.)	31.25 per cent.	Ibid. Jan. 19, 1895. (Hospital.)
45. Tirard and Willcocks.	10	1 (10 per cent.)	38 per cent.	The Lancet, Jan. 19, 1895. (Hospital.)
46. Ruffer.	274	37 (13.5 per cent.)	....	Cases treated in four London hospitals, British Med. Jour., Feb. 2, 1895.
47. Epidemic in Trieste. Cases in private practice.	72	5 (6.5 per cent.)	43.8-62.6 per cent.	Das Oesterreichische Sanitätswesen, Jan. 3, 1895.
48. Cases in hospital.	180	40 (22.2 per cent.)	...	Wiener Klin. Wochenschrift, 1895, No. 3. (Private practice.)
49. Blumenfeld.	50	2 (4 per cent.)	...	Therapeut. Monatshefte, Feb., 1895.
50. Witthauer.	36	5 (14 per cent.)	...	Lyon Médical, Feb. 3, 1895. (Hospital.)
51. Dreyfus.	78	15 (19.3 per cent.)	50 per cent.	La Médecine Moderne, Feb 6, 1895. (Private practice.)
52. Simon.	16	2 (12.5 per cent.)	.. ..	Le Scalpel, Feb. 17, 1895.
53. Malvoz.	15	1 (7 per cent.)	....	Annales des Maladies de l'Oreille, du Larynx et du Pharynx, 1895, No. 5. Abst. in the Medical News, June 15, 1895. (Hospital.)
54. Gougenheim.	125	12 (9.5 per cent.)	21.1 per cent.	Zeitschrift f. Medizinal-Beamte, Feb. 15, 1895. (Collective investigation of use of antitoxin in private practice in district of Minden.)
55. Rapmund.	100	7 (7 per cent.)	20–30 per cent.	Allgem. Med. Central-Zeitung, 1895, No. 88. (Private practice.)
56. Schüller.	32	1 (3.1 per cent.)	....	Abst. Schmidt's Jahrbüch. 1895, Bd. 246, p. 37. (Hospital.)
57. Grünfeld.	12	1 (8.3 per cent.)	....	Berliner Klin. Wochenschrift, 1895, No. 10. (Private practice.)
58. Schaewen.	15	0	....	Ibid. (Private practice.)
59. Heidenhain.	24	3 12.5 per cent.)	....	Deutsche Med. Wochenschrift, 1895, No. 10. (Hospital and private practice.)
60. Risel.	114	9 (7.9 per cent.)	....	Ibid (From private practice of six physicians in Baden.)
61. Weiland.	20	0	....	Correspondenzbl. f. Schweizer-Aerzte, 1895, No 5. (Hospital.)
62. v. Muralt.	58	2 (3.4 per cent.)	...	Abst. in Münchener Med. Wochenschrift, Mar. 5, 1895. (Hospital.)
63. Blattner.	38	9 (23.6 per cent.)	....	Abst. Ibid. (Hospital.)
64. Gerloczy.	55	15 (27.3 per cent.)	....	Rev. Méd. de la Suisse Romande, April 20, 1895. (40 cases in hospital.)
65. D'Espine.	60	6 (10 per cent.)	....	Wiener Med. Blätter, 1895, p. 760. (Hospital.)
66. Mya.	17	2 (11.8 per cent.)	...	Prager Med. Wochenschrift, 1895.
67. v. Engel.	39	10 (25.5 per cent.)	50 per cent.	New York Medical Record, April 6, 1895. (Hospital, consultation and private practice.)
68. Fischer.	225	35 (15.5 per cent.)	...	Ibid. April 20, 1895.
69. Biggs—Cases in the city treated by sanitary inspectors.	255	40 (15.69 per cent.)	25–45 per cent.	Le Bulletin Médical, 1895. No. 21. (Hospital.)
70. Cases in Willard-Parker Hosp'l.	104	45 (27.4 per cent.)	32 per cent.	British Med. Jour., May 18, 1895. (Hospital.)
71. Lennox Browne.	45	2 (4.4 per cent.)	34 per cent.	Ibid. May 11, 1895. (Hospital.)
72. Codd and Whitehouse.	11	4 (36.4 per cent.)	...	Abst. in Münchener Med. Wochenschrift, May 7, 1895. (Hospital.)
73. Winkfield.	22	4 (18.2 per cent.)	36 per cent.	Ibid. May 21, 1895 (abstract). (Hospital.)
74. Horowitz.	21	1 (4.8 per cent.)	10.7 per cent.	The Medical News, June 1, 1895. (Private practice.)
75. Sigel.	100	12 (12 per cent.)	40-50 per cent.	Deutsche Med. Wochenschrift, June 6, 1895. (Hospital.)
76. Howard.	40	3 (7.5 per cent.)	...	Münchener Med. Wochenschrift, June 11, 1895. (Hospital.)
77. Van Nes.	52	12 (23 per cent.)	36–48 per cent.	Deutsche Med. Wochenschrift, July 11, 1895. (35 cases—hospital.)
78. Leichtenstern and Wendelstadt	123	25 (20.3 per cent.)	30.9 per cent.	Abst. in Deutsche Medizinal-Zeitung, June 10, 1895. (Hospital.)
79. Kurth.	97	10 (10.3 per cent.)	....	Abst. in British Med. Jour., July 6, 1895.
80. Timmer.	31	6 (19.4 per cent.)	....	Reported to Assoc. of American Physicians, May 31, 1895. Abst. in the Medical News, June 15, 1895. (Hospital.)
81. Cases treated in Cartagena.	156	21 (13.5 per cent.)	....	
82. Mason.	306	81 (26.4 per cent.)	45-52 per cent.	
TOTAL (82 REPORTS).	7166	1239 (17.3 per cent.)		

The fatality of 7166 cases of diphtheria treated with antitoxin was 17.3 per cent. The previous or simultaneous fatality of cases not treated with antitoxin is stated in 46 reports. These contain 5406 cases treated with antitoxin with 1008 deaths, a fatality of 18.6 per cent. Estimating the number of deaths in these cases upon the basis of the previous or simultaneous fatality for each group (taking the lowest figures given), there would have been 2279 deaths or 42.1 per cent. There was, therefore, an apparent reduction of case mortality by the use of antitoxin of 55.8 per cent.

taneous percentage of deaths from diphtheria not treated with antitoxin is given for the same hospital or locality in which were the cases treated with antitoxin. These reports contain 5406 cases of diphtheria treated with antitoxin, with 1008 deaths or 18.6 per cent. If we calculate the number of deaths in each series of these cases upon the basis of the previous fatality, selecting the lowest percentages given, we have 2279 deaths or 42.1 per cent. There is, therefore, on this estimate by the use of antitoxin an apparent reduction in the number of deaths of 55.8 per cent.

There must be a much greater difference between the characters of the cases composing the two groups compared than appears from the statements of the writers and the details of the cases described, if this striking reduction in fatality is not due to the serum treatment.

If we separate the hospital cases from those in private practice we obtain from 61 reports of Table I 5777 cases of diphtheria treated with antitoxin in hospitals. These furnished 1081 deaths, giving a percentage of 18.7. Although this is not an unheard of fatality of diphtheria in hospitals, it is most exceptional, and I am not aware that anything approaching it has been observed in hospitals receiving large numbers of cases of diphtheria in children. The fourth column in Table I gives the percentages observed in many such hospitals.

There are 41 reports which give for the same hospital the previous percentage of deaths from diphtheria not treated with antitoxin. These furnish 4899 cases treated with antitoxin, with 944 deaths or 19.3 per cent. If we calculate the number of deaths which would have occurred among these cases had the percentages of previous fatality obtained, selecting the lowest percentages given, there would have been 2130 deaths or 43.5 per cent. The apparent diminution in the number of deaths as the result of serum treatment is according to this estimate 55.6 per cent. If we had selected only the larger and most carefully analyzed and satisfactory statistics from the principal hospitals, in large part children's hospitals, there would have been in over 3000 cases an apparent reduction in fatality of 60 per cent.

There may occur considerable differences in the annual fatality from diphtheria in a hospital during a series of years, but such differences between the minimum and the maximum fatality as that just noted between the actual and the estimated fatality are most exceptional. In the Friedrichshain hospital in Berlin there has been observed a difference of 28 per cent. in the annual fatality from diphtheria. The largest difference observed in the surgical clinic in Berlin during ten years was that between 43.2 per cent. in 1888 and 58.5 per cent. in 1890.* In the report of the Metropolitan Asylums Board † in London, where the case mortality from diphtheria in hospitals is generally much lower than on the Continent, the fatality in 1889 was 40.7 per cent.; in 1890, 33.5 per cent.; in 1891, 30.6 per cent.; in 1892, 29.3 per cent.; in 1893, 30.4 per cent. This apparent reduction in fatality since 1889 in large part disappears if only patients under 15 years of age are considered, the corresponding percentages for these being respectively 40.7, 41.6, 36.9, 35.6, and 37.

The natural interpretation of our statistics showing in over 7000 cases, of which at least five-sixths are from hospital practice, treated with antitoxin an extraordinarily low percentage of deaths for this class of cases, and showing an apparent reduction in fatality of from 50 to 60 per cent. by the use of antitoxin, is that antitoxin exerts a specific curative power over diphtheria.

What are the objections which may be and have been urged against this natural interpretation of the statistical evidence? In the first place it has been claimed that these observations have been made during the prevalence of unusually mild diphtheria. In some places the prevailing type of the disease seems to have been mild, but the great majority of the observers quoted in the table consider that the prevailing diphtheria in their localities has been of average severity, and they cite in many instances the simultaneous fatality of cases not treated with antitoxin as proof that the disease is not of peculiarly mild type, indeed in several places it seems to have been of more than average severity. During the period in which Roux treated with antitoxin 300 cases in the Hôpital des Enfants-Malades with a fatality of 26 per cent., the fatality in the Hôpital Trousseau, also in Paris, and receiving a similar class of cases, was 60 per cent.

But even if it be admitted for the sake of argument that the prevailing type of diphtheria during the past year has been mild, it is to be considered that the influence of this milder type upon the cases received in many hospitals appears chiefly in the reduction of their number, and far less in a change in the character of the cases admitted. This is the statement of von Ranke, of Bokai and of several other physicians in charge of diphtheria wards. They say that so far as their hospitals are concerned, as a rule, severe and advanced cases are sent there by physicians in the city, often for operation to relieve laryngeal stenosis, and that when the epidemic is mild in character they receive fewer cases, but not many milder cases. Doubtless these conditions will not hold for all hospitals, particularly not for such as are intended for the compulsory isolation of all cases of diphtheria which cannot be properly isolated at their homes, but they are probably applicable in large part to most of the hospitals from which come the reports now under consideration.

So far as I can judge, no proof has been brought forward in support of the opinion that the low percentage of fatality of diphtheria treated with antitoxin can be referred in any large measure to the prevalence of an unusually mild type of the disease, although in a few scattered groups of cases, particularly some of the smaller series in my table, this may be in part the explanation.

I am inclined to attach decidedly more weight to a second criticism of antitoxin statistics which has been made, namely, that in hospitals where the serum treatment has been carried out, a proportionately larger number of cases are received now than formerly in the earlier stages of diphtheria. The advocates of the treatment have properly insisted upon the importance of early injection of the serum, and, especially during the time when the serum was not to any extent in the

* V. Hirsch. Archiv f. klin. Chirurgie, Bd. 49, Hft. 4.

† British Medical Journal, Dec. 22, 1894.

hands of general practitioners, it would be natural to suppose that physicians would send their patients and parents take their children to such hospitals as soon as possible after recognition of the disease. Inasmuch as with any approved method of treatment of diphtheria the results are better the earlier it is begun, it is evident that statistics based on the former experience with the treatment of diphtheria in hospitals would not be altogether comparable with the antitoxin statistics from the same hospitals.

It is, however, very difficult to say how much allowance is to be made for this criticism. There has been wide-spread skepticism among physicians and the general public as to the value of the treatment. Thus Rapmund, in his efforts to establish in the district of Minden a collective investigation of serum therapy in diphtheria, found the physicians so skeptical that of 194 practitioners only 20 would use it at all, and only two employed it extensively. There are also statements as to the unwillingness of parents to have it tried on their children. Many of the reports state that during the period of serum treatment cases were not received in any earlier stages of the disease than formerly; in a few of the reports, as for example in that of Kuntzen from Oschersleben, it is said that physicians were induced to send their patients early in the disease. In Berlin and some other cities there has been a marked increase in the number of patients with diphtheria admitted to hospitals since the introduction of the antit xin treatment, and this has been without a corresponding increase in the total number of cases in the cities. Heubner in his recent address at the Congress of Internal Medicine in Munich admits that lighter cases of diphtheria go to the hospital now, but that this is not enough to explain the great difference in fatality. There are undoubtedly considerable differences in different hospitals as to the proportion of cases admitted in early stages of diphtheria, but in many of the hospitals where the benefits of antitoxin have been most apparent as contrasted with the previous results it is expressly stated that the number of mild cases admitted is no greater than formerly.

If we make all due allowance for this possible increase in the proportion of early cases treated in hospitals, and certainly some allowance must be made, this factor is still altogether inadequate to explain the great reduction in fatality of diphtheria treated with antitoxin. This will also be apparent later when we consider the results of treatment according to the day of the disease on which it is begun.

A third criticism, namely, that the bacteriological control of the diagnosis of diphtheria operates in favor of a low mortality in antitoxin statistics, has already been fully discussed.

It is manifestly improper to compare the average fatality of thousands of cases treated in hospitals with antitoxin with exceptionally favorable results at certain periods in a few hospitals in a comparatively small number of cases without serum treatment, and still more improper, as has even been done, to make such comparison with the most favorable percentages which one can find reported from private practice or in municipal mortality statistics. Surely some consideration must be given to the previous and simultaneous results obtained from cases without serum treatment in the same hospitals from which the cases reported are derived.

We have now considered the principal objections which have been made to the natural interpretation of statistics showing an apparently great reduction in the fatality of diphtheria by the use of antitoxin. I believe that it has been shown that even if all possible allowance be made for such assumptions as those considered, they are still wholly inadequate to account for an apparent reduction in the deaths from diphtheria by antitoxic treatment of 50 to 60 per cent. in nearly 5000 cases collected from hospitals in Germany, France, Austria, Italy, England and America, and reported by forty different physicians, most of whom are of high reputation and large experience. These statistics seem to me to establish beyond all reasonable doubt the conclusion that antitoxin is a specific curative agent for diphtheria.

It has been contended that the only absolutely convincing proof of the curative efficacy of antitoxin is the demonstration of a marked reduction in the total number of deaths from diphtheria in a city or town in proportion to all of the cases. Municipal mortality and morbidity statistics are necessarily far less accurate than hospital statistics, and for reasons which have been stated, the prevalence of a mild type of diphtheria will have greater influence upon municipal mortality statistics for diphtheria than upon hospital statistics. It is to be expected that when sufficient time has elapsed and the employment of antitoxin in the treatment of diphtheria has become sufficiently general, the reduction in fatality by its use will be apparent in general fatality statistics. At present we have little information upon this point. The mere statement of the total number of deaths, without knowledge of the morbidity and of the prevailing type of disease, is of course not decisive for either side of the question, but so far as it goes it is interesting to learn that in Boston during the antitoxin period (January 1 to May 1, 1895) the total fatality from diphtheria was 14 per cent., as compared with a fatality of 31 per cent. during the corresponding period of previous years (Mason), and that in Cartagena, Spain, during four months of employment of antitoxin, the total number of deaths was only one quarter the average number for the same period of time during the preceding ten years.

The only antitoxin statistics which I can find based upon such material as composes municipal fatality statistics are those of Risel and of Kurth.

Risel reports the results in all of the cases treated by antitoxin during two months in the city of Halle. They are derived from the practice of thirty physicians among the poor and the rich, in the houses of the patients and in hospitals, and include mild and severe cases as they presented themselves. Of the 89 patients treated in their homes, almost without exception children not over 7 years of age, 6 died, giving a fatality of 6.7 per cent. 19 of these had laryngeal diphtheria, of whom 4 died. Of the 25 patients treated in hospitals, 3 died, a fatality of 12 per cent. 15 of these had laryngeal involvement, of whom 3 died. The total fatality was 7.9 per cent. No data are given for comparison with the previous or simultaneous fatality of cases not treated with serum. In only a few cases, and these in hospitals,

was the clinical diagnosis confirmed by bacteriological examination.

Kurth reports the results of serum treatment in the practice of sixty physicians in Bremen and a few outlying villages from October 8, 1894, to January 31, 1895. A circular letter was sent from the Bacteriological Institute to every physician in the city, and apparently general co-operation on the part of the physicians and the public officials was secured. In 97 cases treated with serum the diagnosis of diphtheria was established, in the great majority of cases by demonstration of the Löffler bacillus controlling the previous clinical diagnosis. The total case mortality was 10.3 per cent. The fatality of the 64 cases treated in the city (hospital and private practice) was 7.8 per cent.; that of 33 cases derived from the surrounding country district was 15.2 per cent.; that of 35 cases treated in the city hospitals was 14.3 per cent. Laryngeal diphtheria occurred in 66 per cent. of the cases in country districts and only in 36 per cent. of the cases in the city. This and the generally less favorable results in country practice are attributed by Kurth not to greater severity of the epidemic in the former, but to the custom in the country of not calling the physician until the symptoms are urgent, and to the greater distance which the physicians have to travel. If the bacteriological control of the diagnosis be disregarded, that is, if all the cases diagnosed clinically as diphtheria and treated with serum be considered, the fatality was 9.4 per cent., another illustration that bacteriological control of the clinical diagnosis results in higher, not as some have claimed in lower, percentage of deaths. Of the 50 cases of clinical diphtheria, all of the cases being included which did not show Löffler bacilli, the fatality was only 6 per cent. During the serum period there occurred 25 cases of diphtheria not treated with antitoxin, with a fatality of 24 per cent. During the same period of the year in which the serum-treated cases occurred, there were during the preceding year 148 cases of diphtheria with a fatality of 32 per cent. It must be conceded that these interesting reports of Risel and of Kurth speak strongly in favor of the possibility of bringing about a great reduction in the general fatality from diphtheria in cities by treatment with antitoxin. As a larger proportion of the cases in private practice can be treated in early stages of the disease than in the hospitals, this reduction should be greater than that already shown by hospital statistics.

A most convincing demonstration of the healing power of antitoxin is furnished by the experience of Baginsky during an involuntary pause in the serum treatment caused by failure in the supply of serum. Between March 15, 1894, and March 15, 1895, there were treated in Baginsky's service by antitoxin 525 children with a fatality of 15.6 per cent. During the period of forced interruption of the serum treatment, this period being chiefly the months of August and September, 126 children were treated without antitoxin, with a fatality of 48.4 per cent. There was absolutely no selection of cases in either group. In his comments upon this experience Baginsky says: "It is all the more remarkable, as the ratio of mortality of those treated with the serum both before and after the period of interruption varied within very small percentage figures. If one will permit figures to speak at all, there has scarcely been made on human beings a more demonstrative test of the curative power of a therapeutic agent. It was an experiment forced upon us, but it proved to us how terrible was the form of disease which we were treating, and how numerous would have been the victims without the use of the healing serum."

A similar experience has been reported by several other writers. Thus Körte noted a rise in fatality from 33.1 per cent. during the serum period to 53.8 during the period of failure in the supply of serum. Ganghofner, under similar conditions, a rise from 12.7 per cent. to 53.2 per cent.; Heim, from 22 per cent. to 65.6 per cent., and during the epidemic in Trieste the fatality rose from 18.7 per cent. to 50 per cent. when the serum failed. All of these highly significant observations were made on cases occurring in the same epidemic, the period of enforced interruption of the serum treatment being preceded and followed by the periods of serum treatment.

We have considered thus far mainly the hospital statistics. These are for manifest reasons more numerous, larger and more carefully analyzed than those from private practice. It is, however, in private practice, especially among those classes who are in the habit of calling the physician early in the disease, that the best results from serum treatment are to be expected, for here there is more frequent opportunity for timely treatment. A glance at Table I will show that in general the fatality of diphtheria treated with serum in private practice is much lower than in hospitals.

If we summarize the 18 reports from private practice in Table I we have 663 cases of this class treated with antitoxin, and among these are 46 deaths, giving a fatality percentage of only 6.9. This would indicate that the serum treament may reduce the fatality from diphtheria in private practice to nearly one-third that under the same treatment in hospitals. Some of the reports of the results of serum treatment in private practice furnish, indeed, most remarkable evidence of the efficacy of this treatment.

Most of the reports attempt some sort of classification of the cases treated with antitoxin. The simplest and most common, although not the most valuable, is the division according to degrees of apparent severity, expressed by such epithets as mild, moderate, severe, very severe. Such a classification is, of course, only of limited value, as even the mildest case of diphtheria may unexpectedly assume a malignant character. If, as we believe to be proven, antitoxin injected in time arrests the local process and the constitutional disturbance, then many of the cases which appear under the head of mild cases in antitoxin statistics would under other methods of treatment have become severe cases and would be so recorded. Indeed, with the early administration of antitoxin there should be comparatively few severe cases.

The classification of diphtheria adopted by Roux into angina and croup, with and without microbic association, has been followed by some of his successors. So far as this classification is actually based upon a correct separation of pure diphtheria from diphtheria with mixed infection, it is of the utmost importance in determining the relative value of antitoxin in the treatment of these two divisions of diphtheria.

I have already expressed the opinion, however, that the bacteriological examination of the exudate and secretions in the throat is not decisive in determining the presence or absence of mixed infection. Still Roux's analysis of his cases on this basis indicated clearly that the serum was far more efficacious in diphtheric anginas and croup which yielded pure cultures of the Löffler bacillus than in those which gave, in addition to the Löffler bacillus, cultures of other pathogenic bacteria. In presenting these results the epithet "pure" applied to angina or croup is to be understood to signify that only the Löffler bacillus was found in the cultures, and the epithet "associated" to signify that this bacillus was found in cultural association with the coccus of Brisou, staphylococci or streptococci, most commonly the last. The "corrected" percentages are those obtained after subtracting deaths occurring within twenty-four hours after admission.

Of the 300 cases treated with serum with a total fatality of 26 per cent. reported by Roux, Martin and Chaillou, there were 120 pure anginas, fatality 7.5 per cent. (corrected 1.7 per cent.); 49 associated anginas, fatality 24.2 per cent. (corrected 17.7 per cent.); of not operated croup, 4 pure, fatality 0, 6 associated, fatality 16.6 per cent.; of operated croup, 49 pure, fatality 30.9 per cent. (corrected 24.4 per cent.), and 72 associated, fatality 56.9 per cent. (corrected 43.1 per cent.).

Of Moizard and Perreganx's 231 cases, total fatality 14.7 per cent., there were 44 pure anginas, fatality 4.5 per cent.; 42 associated anginas, fatality 14.3 per cent.; 94 pure croup, fatality 18.5 per cent.; 51 associated croup, fatality 17.6 per cent. No correction is made in these percentages.

Of Sevestre and Meslay's 150 cases, total fatality 10 per cent., there were 29 pure anginas, fatality 3.4 per cent.; 24 associated anginas, fatality 12.5 per cent. (corrected 8.3 per cent.); 67 pure croup, fatality 8.9 per cent. (corrected 7.5 per cent.); 30 associated croup, fatality 16.6 per cent. (corrected 6.6 per cent.).

It will be observed that in the last two reports the excess in fatality in the "associated" diphtherias is much less striking than in Roux's statistics, and in some cases disappears altogether. This I am inclined to attribute to failure of the method employed to indicate properly the division into pure and mixed infections, for the testimony is unanimous that the serum is of far less benefit in mixed diphtheria than in uncomplicated diphtheria, the most common and dangerous complicating micro-organism being the streptococcus pyogenes.

Most noteworthy has been the improvement in the results of serum therapy of diphtheria in the Paris hospitals since Roux's original communication to the Congress in Budapest in September, 1894. The fatality has descended from Roux's original percentage of 26, in the later reports to 14.7, 12 and 10 per cent., and according to a recent statement of Moizard and Bouchard (July, 1895), it at present oscillates between 8 and 14 per cent. These are the best results which have hitherto been reported from any hospital for any large number of cases, and they are certainly most significant. As Moizard and Bouchard in their recent communication say, "This result can no longer be attributed to fortunate series of cases, as was claimed at the beginning by adversaries of the method. Thousands of patients have been treated, and it can now be said that the controversy is closed." This striking descent from Roux's first figures is not, however, attributed by the writers wholly to improvements in the methods of serum therapy. As Roux pointed out in his first paper, the hygienic conditions in the two Paris hospitals from which these statistics come were very bad. These conditions have since then been greatly improved, and this reform has been especially manifest in the reduction of the deaths from bronchopneumonia.

A most important classification of diphtheria for estimating the curative value of antitoxic serum is that into cases without and with laryngeal stenosis, and especially when such degrees of stenosis are considered as require operative interference by tracheotomy or intubation. I have therefore prepared the following table (Table II) which gives the results of antitoxin treatment in operated and not operated cases of diphtheria. This of course is not equivalent to a division into anginas and croup, as many cases of croup are included in the non-operated cases, but I have desired to submit the new method of treatment to the most severe test. No one can claim that laryngeal diphtheria requiring intubation or tracheotomy is anything but a severe disease. If the benefits of antitoxin are unmistakably manifested in these operated cases of croup, then the test is an *experimentum crucis* and puts an end to the objections of those who assert that the apparently favorable results of serum therapy in diphtheria are attributable mainly to the large proportion of mild cases treated.

The same reports with a few additional ones, for which references are given, have been used for Table II as for Table I, but many of the reports in Table I were not available for this table, as the writers did not always present their results in a form which fitted into the classification adopted. The table gives for each report the total number and fatality of cases treated, as in Table I, the number and fatality of cases not operated on (including cases of croup), the number and fatality of cases operated on, "T" signifying tracheotomy, "I" intubation, "I and T" signifying intubation followed by tracheotomy, and, so far as reported, the previous or simultaneous percentage of fatality from operation in cases not treated with antitoxin. In the final column are pertinent statements concerning cases in the series. Some reports are inserted which do not give the number of cases under the different headings. These, of course, cannot be used in the summary giving the totals.

Of the 4294 cases in Table II, 27.2 per cent. required tracheotomy or intubation. There were, however, many more cases of laryngeal diphtheria in this group than the ratio of operative cases would indicate, for it is the testimony of the great majority of the observers that the stenotic symptoms of laryngo-tracheal diphtheria are relieved without the necessity of operation in a much larger proportion of the cases treated with antitoxin than by any other method of treatment. As is well known, recovery without intubation or tracheotomy from descending laryngo-tracheal diphtheria, especially in children, is exceptional under all other methods of treatment, and the greater relative frequency with which such recovery occurs under serum treatment is a strong proof of the efficacy of antitoxin.

TABLE II.—FATALITY IN OPERATED AND NON-OPERATED CASES OF DIPHTHERIA TREATED WITH ANTITOXIN.

T Signifies Tracheotomy, *I* Intubation, *I* and *T* Intubation followed by Tracheotomy.

Reporter.	Total Cases.	Deaths.	Not Operated Cases.	Deaths.	Operated Cases.	Deaths.	Previous Fatality from Operation.	Remarks.
Roux, Martin and Chaillou.	300	78 (26 per cent.)	179	22 (12.8 per cent.)	121 *T*	56 (46 per cent.)	67 per cent.	Deducting those which died in less than 24 hours after admission to the hospital, there remain 107 tracheotomies with 42 deaths (39.2 per cent.).
Kossel.	117	13 (11.1 per cent.)	94	1 (1.1 per cent.)	23 *T*	12 (52.2 per cent.)	....	In all of the fatal operations it was necessary to perform tracheotomy within 12 hours after admission.
Körte.	121	40 (33.1 per cent.)	79	18 (22.8 per cent.)	42 *T*	22 (52.4 per cent.)	77.5 per cent.	Of 8 tracheotomized cases under 2 years of age, 5 died (62.5 per cent.). The previous fatality for tracheotomy under 2 years was 90.7 per cent.
Sonnenburg.	95	16 (16.8 per cent.)	61	8 (13.1 per cent.)	34 *T*	8 (23.5 per cent.)	38 per cent.	The fatality of 38 per cent. in the table is that of 47 tracheotomies performed during the period in which the supply of antitoxin temporarily was exhausted and could not be at once replaced.
Baginsky.	525	83 (15.6 per cent.)	450	47 (10.9 per cent.)	95 (53 *T*) (54 *I*) (In 12 cases tracheotomy followed intubation.)	36 (34 *T*) (37.8 p. c.) (2 *I*) (Of the secondary tracheotomies 12 died.) (37.9 per cent.)	64.4 per cent. *T* 44.8 per cent. *I*	During two months in which the supply of serum failed the general fatality rose to 48.4 per cent. and that from tracheotomy and intubation to 62.2 per cent. The fatality at once fell upon re-introduction of the antitoxin treatment.
v. Widerhofer.	300	71 (23.7 per cent.)	192	20 (10.4 per cent.)	108 *T* or *I*	51 (47.2 per cent.)	....	22 cases of laryngeal diphtheria (croup) recovered without operation
v. Ranke.	96	19 (19.7 per cent.)	54	6 (11.1 per cent.)	42 *I*	13 (30.9 per cent.)	61-75 per cent.	21 cases of croup recovered without operation.
Stintzing.	59	12 (20.1 per cent.)	43	5 (11.6 per cent.)	16 *T*	7 (44 per cent.)	49 per cent.	.....
Schröder.	63	8 (12.7 per cent.)	32	5 (15.6 per cent.)	31 *T*	3 (9.67 per cent.)	....	.....
Vierordt.	63	16 (25 per cent.)	48	9 (18.75 per cent.)	15 *T*	7 (46 per cent.)	....	Deducting 8 cases in a hopeless condition on admission, there was only one death among the non-tracheotomized cases, a death rate of only 2.7 per cent.
Rumpf.	22	2 (8 per cent.)	15	0	7 *T*	2 (28.6 per cent.)	....	
Lebreton and Magdelaine.	258	31 (12 per cent.)	184	8 (4.4 per cent.)	75 (24 *T*) (51 *I*)	25 (9 *T*) (37.5 p. c.) (14 *I*) (27.5 p. c.)	73.2 per cent. *T*	Of the intubated cases 7 died in less than 24 hours after admission. Deducting these, the fatality from intubation was only 18.1 per cent.
Legendre Moizard & Perreaux Sevestre and Meslay.	398	52 (13.1 per cent.)	316	23 (7.6 per cent.)	(51 *T*) 82 (21 *I*) (10 *I* & *T*)	(20 *T*) (39.2 p. c.) 29 (5 *I*) (23.8 p. c.) (4 *I* & *T*) (40 p. c.) (35.4 per cent.)	86 per cent. *T*	Deducting 15 deaths in less than 24 hours after admission, the total fatality is reduced to 9.7 per cent. These cases are those treated in the Hôpital Trousseau in Paris from the middle of Sept. to Dec. 25, 1894.
Ganghofner.	110	14 (12.7 per cent.)	66	8 (12 per cent.)	44 *I* or *T*	6 (13.6 per cent.)	59.8-78 per cent.	12 laryngeal diphtherias recovered without operation. During period in which the supply of serum failed the general fatality rose to 53.2 per cent. and that of operated cases to 68.9 per cent.
Soltmann.	89	13 (14.6 per cent.)	48	2 (4.2 per cent.)	41 *I*	11 (27 per cent.)	68 per cent.	.....
Bokai.	120	31 (25.5 per cent.)	71	10 (14 per cent.)	49 *I*	21 (43 per cent.)	70 per cent.	In 14 cases presenting symptoms of moderate laryngeal stenosis upon admission, these symptoms disappeared after injection of antitoxin without operation.
Heim.	27	6 (22 per cent.)	21	4 (19 per cent.)	6 (2 *T*) (4 *I*)	2 (1 *T*) (50 per cent.) (1 *I*) (25 per cent.) 33.3 per cent.	....	During period when supply of serum failed the general fatality rose to 65.6 per cent. Heim treated altogether 48 cases in two groups, but of his 2d group of 21 cases 12 were still under treatment at date of report and these are not included in my table.
Börger.	30	2 (6.66 per cent.)	25	1 (4 per cent.)	5 *T*	1 (20 per cent.)	....	313 cases of diphtheria treated in the same hospital (Greifswald) from Oct., 1893, to Sept., 1894, gave a fatality of only 14.5 per cent.
Moeller.	76	27 (35.5 per cent.)	28	8 (28.6 per cent.)	48 *T*	19 (39.6 per cent.)	55.6 per cent.	.....
Kuntzen.	25	3 (12 per cent.)	20	1 (5 per cent.)	5 *T*	2 (40 per cent.)	....	.....
Charon.	13	4 (30.8 per cent.)	2	0	11 *T*	4 (36.4 per cent.)	....	.....
Washbourn, Goodall and Card.	72	14 (19.4 per cent.)	63	11 (17.5 per cent.)	9 *T*	3 (33.3 per cent.)	91.7 per cent.	In 13 previous series of tracheotomies in each group the average of deaths numbered 8¾.
Herringham.	18	3 (16.7 per cent.)	7	0	11 (10 *T*) (1 *I*)	3 (30 per cent. *T*)	65 per cent. *T*	The 7 unoperated cases were mild.
Germonig—(Civic Hospital of Trieste.)	224	42 (18.7 per cent.)	178	18 (10 per cent.)	46 (2 *T*) (44 *I*)	24 *I* (54.5 per cent.)	85.5 per cent. *T* 75 per cent. *I*	During a period of exhaustion of the supply of serum the general fatality rose to 50 per cent. These data are from abstracts in the British Med. Jour., Feb. 2, 1895, and the Deutsche Med. Wochenschrift, 1894, No. 52. The general serum fatality is variously given as 18.7 per cent., 20.3 per cent. and 22 per cent.
Witthauer.	36	5 (14 per cent.)	16	1 (6.25 per cent.)	20 *T*	4 (20 per cent.)	25 per cent.	Only one adult in this series.
Rapmund.	100	7 (7 per cent.)	98	7 (7.1 per cent.)	2 *T*	0	....	Collection of cases treated in private practice by several physicians in Minden.
Heidenhain.	24	3 (12.5 per cent.)	22	2 (9.1 per cent.)	2 *T*	1 (50 per cent.)	....	.....
Risel.	114	9 (7.9 per cent.)	95	5 (5.3 per cent.)	19 *T* (14 *I*)	4 (21 per cent.)	....	.....
v. Muralt.	58	2 (3.4 per cent.)	38	0	20 (2 *T*) (4 *I* and *T*)	2 (10 per cent.)	....	After intubation (14 cases) no death. after intubation and tracheotomy 1 death. after tracheotomy 1 death.
D'Espine.	60	6 (10 per cent.)	49	2 (8.2 per cent.)	11 *T*	4 (36.4 per cent.)	....	10 cases of croup recovered without operation.
v. Engel.	30	10 (25.5 per cent.)	20	7 (23.3 per cent.)	9 *T*	3 (33.3 per cent.)	85 per cent.	The fatality of 42 unoperated cases not treated with antitoxin was 33.4 per cent., that of 20 tracheotomized cases not so treated was 85 per cent.
Codd & Whitehouse.	11	4 (36.4 per cent.)	7	2 (28.6 per cent.)	4 (3 *T*) (1 *I*)	6 *I* 2 *T* (66.6 per cent.) 50 per cent. of operated cases.	....	3 of the 4 deaths were from croup.
Winkfield.	22	4 (18.2 per cent.)	19	2 (10.5 per cent.)	3 *T*	2 (66.6 per cent.)	85.7 per cent.	.....
Sigel.	100	12 (12 per cent.)	No. of cases not given.	...	No. of cases not given.	20.3 per cent. *T*	63.3 per cent. 70 per cent.	The fatality of tracheotomized cases in 1894 up to the date of beginning treatment (Oct. 4) was 70 per cent., after treatment with antitoxin 20.3 per cent.
Galatti.	No. of cases not given.	....	No. of cases not given.	....	15 *I*	6 (40 per cent.)	52.6 per cent. *I*	Quoted in Le Bulletin Médical, 1895, p. 364.
Kraske.	Not given.	....	....	....	16 *T*	5 (31.25 per cent.)	28 per cent (in 12 cases).	Says that he has tracheotomized 12 cases not treated with antitoxin, with a fatality of only 28 per cent. Abst. in Münchener Med. Wochenschrift, 1894, p. 1062.
Bonain.	Not given.	....	....	....	5 *I*	2 (40 per cent.)	60.5 per cent.	Le Bulletin Médical, April 17, 1895.
Van Nes.	52	12 (23 per cent.)	30	4 (13.3 per cent.)	22 (15 *T*) (7 *I*)	8 (36 per cent. *I* & *T*)	48-73 per cent.	During ten preceding years the lowest fatality of operated cases was 52 per cent., of not operated 16 per cent. In 3 groups of 92 cases each preceding the introduction of antitoxin treatment, the lowest fatality of operated cases was 48 per cent., of not operated cases

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	.....
Sigel.	100	12 (12 per cent.)	No. of cases not given.	...	No. of cases not given.	20.3 per cent. *T*	63.3 per cent. 70 per cent.	The fatality of tracheotomized cases in 1894 up to the date of beginning treatment (Oct. 4) was 70 per cent., after treatment with antitoxin 20.3 per cent.
Galatti.	No. of cases not given.	....	No. of cases not given.	....	15 *I*	6 (40 per cent.)	52.6 per cent. *I*	Quoted in Le Bulletin Médical, 1895, p. 364.
Kraske.	Not given.	....	....	....	16 *T*	5 (31.25 per cent.)	28 per cent (in 12 cases).	Says that he has tracheotomized 12 cases not treated with antitoxin, with a fatality of only 28 per cent. Abst. in Münchener Med. Wochenschrift, 1894, p. 1062.
Bonain.	Not given.	....	.. .	....	5 *I*	2 (40 per cent.)	60.5 per cent.	Le Bulletin Médical, April 17, 1895.
Van Nes.	52	12 (23 per cent.)	30	4 (13.3 per cent.)	22 (15 *T*) (7 *I*)	8 (36 per cent. *I* & *T*)	48-73 per cent.	During ten preceding years the lowest fatality of operated cases was 52 per cent., of not operated 16 per cent. In 3 groups of 92 cases each preceding the introduction of antitoxin treatment, the lowest fatality of operated cases was 48 per cent., of not operated cases 19 per cent.
Leichtenstern and Wendelstadt.	123	25 (20.3 per cent.)	86	9 (10.4 per cent.)	37 *T*	16 (43.2 per cent.)	64 per cent.	Of 17 tracheotomized cases less than 2 years old 9 died, between 2 and 4 years 4 out of 11 died; of 13 unoperated cases under 2 years 2 died; of 21 between 2 and 4 years 2 died.
Kobts.	39	Not given.	Not given.	9.1 per cent.	Not given.	30.77 per cent. *T*	...	Abst. Münchener Med. Wochenschrift, June 11, 1895.
Timmer.	31	6 (19.4 per cent.)	25	5 (20 per cent.)	6 *T* or *I*	1 (16.6 per cent.)	....	.....
Mason.	306	81 (26.4 per cent.)	275	62 (22.5 per cent.)	31	19 (61 per cent.)	90 per cent.?	The statement is that the mortality from tracheotomy was reduced by the antitoxin about one-third.
Kurth.	97	10 (10.3 per cent.)	82	7 (8.5 per cent.)	15 *T*	3 (20 per cent.)	....	Of 32 cases of laryngeal diphtheria not operated upon, 30 recovered.
Total of 38 Reports.	4294	784 (18.3 per cent.)	3127	350 (11.2 per cent.)	1167	434 (37.2 per cent.)		Of the total cases 27.2 per cent. were operated upon by tracheotomy or intubation.

In 41 *reports there are* 648 *tracheotomies with* 258 *deaths, a fatality of* 39.8 *per cent.;* 342 *intubations with* 99 *deaths, a fatality of* 28.9 *per cent., and* 26 *intubations followed by tracheotomy with* 14 *deaths, a fatality of* 53.8 *per cent.*

There are 211 *operated cases in which it is not stated how many are tracheotomy or intubation. These gave a fatality of* 40.2 *per cent. They were probably for the most part tracheotomies.*

The reports giving the previous or simultaneous fatality from tracheotomy contain 510 *cases of tracheotomy with* 217 *deaths or* 42.5 *per cent. If the fatality of these cases be reckoned on the basis of the preceding or simultaneous fatality, selecting the lowest figures given, there would have been* 329 *deaths or* 64.5 *per cent. There was, therefore, an apparent reduction in fatality of* 34.1 *by the serum treatment.*

Making a similar estimate on the basis of previous fatality from intubation, there were 250 *intubations with* 79 *deaths or* 31.6 *per cent. instead of* 156 *deaths or* 62.4 *per cent. There was, therefore, an apparent reduction in the fatality of intubated cases of* 49.5 *per cent. as the result of serum treatment.*

The fatality of 3127 *non-operated cases was only* 11.4 *per cent.*

Of Kossel's 44 cases of laryngeal diphtheria treated with antitoxin, 21 (47.7 per cent.) recovered without operation; of von Widerhofer's 130 stenotic cases treated with serum 22 (16.9 per cent.) recovered without operation; of von Ranke's 63 cases, 21 (33.3 per cent.); of Vierordt's 24 cases, 9 (37.5 per cent.); of Ganghofner's 56 cases, 12 (21.4 per cent.); of Bokai's 63 cases, 14 (22.2 per cent.); of d'Espine's 21 cases, 10 (47.6 per cent.). Von Ranke says that before the use of serum at most 5 per cent. of his cases of laryngeal stenosis escaped operation, whereas now 33 per cent. escape. Of Ganghofner's stenotic cases formerly 12 per cent. escaped operation, whereas now 21 per cent. escape. The experience of Heubner and many others is similar.

In this respect, as in so many others, the results in the Paris hospitals have been most favorable. Of Moizard and Perregaux's 145 cases of croup, 90 (62.1 per cent.) recovered without intubation or tracheotomy. Roux, Martin and Chaillou say, "Of 169 children, admitted to the service for diphtheric angina, 56 presented laryngeal symptoms; 31 had hoarse voice, and in 25 the voice was so far extinguished and the dyspnœa (*tirage*) so marked that one might believe that the latter patients should be operated on. Under the influence of the serum (and in these cases one should not fear to make an injection every twelve hours), the dyspnœa diminished, then occurred only paroxysmally, the child coughed up false membranes, and at the end of two or three days the respiration became normal, to the great astonishment of the interns and personnel of the pavilion who, with their large experience of children affected with croup, indeed thought that operation could not be avoided. To-day in the presence of a child with dyspnœa it is not necessary to press for operation. One can inject the serum and wait as long as possible. Since the introduction of the serum the number of tracheotomies in the pavilion has diminished."

Out of his large experience Baginsky expresses himself in these vigorous words: "Here again the observation of the individual cases of laryngeal stenosis, and more especially of those which do not come to the point of operation, speak to me more forcibly than the statistical figures. The surprising regression of the laryngo-stenotic respiratory phenomena, the freedom of breathing, the disappearance of the hoarse voice and the croupy cough, the euphoria of the children, the change in their general condition so that two days after the injection they are sitting up in bed, playing and contented and observant of their surroundings; all of these things produce in him who has had before his eyes for years the hopeless picture of continually progressing laryngeal stenosis, in very truth ineffaceable impressions."

Experience based upon such a large number of cases and careful clinical observation must be regarded as representing the norm. That there may be deviations from this norm, even in a fair number of cases, seems to be illustrated by the experience of Leichtenstern and Wendelstadt, who in 123 cases of diphtheria, with 37 tracheotomies, were not able to note any material reduction in the proportion of cases requiring tracheotomy as compared with former series of cases. Their observations were uncontrolled by bacteriological diagnoses.

Another point to be considered in this connection is of capital importance as an indication of the value of serum treatment. Cases which are free from symptoms of laryngeal involvement at the time of injection of the serum do not develop such symptoms later, or do so only very exceptionally, unless evidences of such involvement appear within twenty-four hours after the injection.

Regarding neither this nor any other point is there entire unanimity of opinion in the various reports, nor is such to be expected from observers of limited numbers of cases with unequal distribution in the various groups of mild cases, of early cases, of anginas, of croup, of pure diphtheria, of septic diphtheria, etc., to say nothing of the absence in some reports of any bacteriological control of the diagnosis and of treatment by insufficient doses or inferior quality of serum. I am only surprised that the conflicting statements are not more numerous. But there are not many points concerning which there are so few differences of statement as concerning the efficacy of antitoxin in preventing descent of the diphtheritic process to the larynx and the trachea. Over and again one can read in the reports such statements as that in all of the patients who entered without laryngeal diphtheria, the larynx remained free, or that unless the symptoms of stenosis appeared within the first twenty-four hours after injection of the serum, they were not observed at all or only most exceptionally. Among the many vouchers for these statements may be cited Kossel, Roux, Baginsky, von Widerhofer, Heubner, von Ranke, Vierordt, Ganghofner, Escherich, Bokai, Van Nes, Kurth.

It is this power of antitoxin to check the spread of the diphtheritic process from the tonsils and pharynx into the larynx, and from the larynx into the bronchi, which has impressed many observers in favor of the new treatment more forcibly than any other feature of their experience with its action. Thus Vierordt observed that of 24 children with diphtheria who were admitted with unaffected larynx and treated with antitoxin, only one developed temporarily a hoarse cough on the third day. In all of the others the larynx remained free. Of 23 patients who were admitted with unaffected larynx not long before the introduction of the serum treatment, nine afterward developed croup. This is doubtless a somewhat unusual experience as regards the large proportion of cases of croup developing under previous methods of treatment.

It follows from what has been said that the ratio of operative cases in antitoxin statistics will in general be smaller than in statistics of cases of the same character treated by other methods. On the one hand there will be fewer laryngeal stenoses developing after commencement of the treatment, and on the other hand a larger number of recoveries from laryngeal diphtheria without the necessity of operation.

The following figures serve to illustrate this point. In the service from which the cases reported by Roux were derived, tracheotomy was performed before the serum period in 50 per cent. of the cases of diphtheria, after the introduction of serum in 40 per cent. The later Paris reports give a much greater reduction in the ratio of tracheotomies. In Baginsky's service 43.9 per cent. of the cases were operated on before the use

of serum, and 18.1 per cent. after its introduction; in von Ranke's service the corresponding figures are 57 per cent. before and 43.5 per cent. after; in Bokai's 65.6 per cent. before and 40.8 per cent. after. As already mentioned, Leichtenstern's figures, 32 per cent. before and 30 per cent. after serum, are exceptional.

It is furthermore to be considered that in view of the power of antitoxin to abate beginning and moderate symptoms of stenosis, operation will be delayed rather than hastened, and, when performed, the indications for it will generally be urgent. For manifest reasons, most of the operations will fall within a period not remote from the time of injection of the serum. Of the 121 tracheotomies in the report of Roux, Martin and Chaillou, 102 were performed either before the first injection of antitoxin or within 12 hours afterward; 14 between the 12th and the 36th hour after inception of the serum treatment, and only 5 later than 36 hours after the injection of the serum. Of the 23 tracheotomies with 12 deaths reported by Kossel, the operation was performed within the first twelve hours in all of the fatal cases, and of the 11 successful cases it was performed in 9 on the day of admission to the hospital, in 1 on the second day and in 1 on the following day. Kossel refers the increase in the stenotic symptoms after injection of the serum in the two last cases to the separation of the false membranes, a point to which others have also called attention as an effect of antitoxin and which is to be borne in mind in cases of croup treated by antitoxin.

Turning now to the results of tracheotomy and intubation in cases treated with antitoxin, we find in Table II that in 41 reports there were 648 tracheotomies with 258 deaths, a fatality of 39.8 per cent., and 342 intubations with 99 deaths, a fatality of 28.9 per cent., and 26 intubations followed by tracheotomy with 14 deaths, a fatality of 53.8 per cent. These are not unheard of fatalities from these operations, but they are so low as to indicate decidedly remedial action of antitoxin.

The percentage of fatality from tracheotomy in diphtheria given by Monti from a total of 12,736 cases up to 1887 is 73.3. The percentage given by V. Hirsch in 1654 tracheotomies in diphtheria, in von Bergmann's clinic in Berlin during the last ten years and seven months (up to July 31, 1894), is 68.7, the fatality during the first four years of this period being 70.5 per cent., and during the last four years 63.8 per cent. The fatality during the first year of life was 98.8 per cent. and sank for each year to the ninth, when it was 41.7, and after the tenth year it rose again.

More proper, however, than comparison with these latter percentages is comparison with the percentages of fatality in the same hospital or place from which the respective groups of cases are reported. It will be observed that with one exception in the table the percentage of deaths following operation in cases treated by antitoxin is lower, and generally very much lower, than the previous or simultaneous fatality. Kraske's exceptional series is of so few cases (only 5 with and 12 without serum) as to be without any significance. The lowest fatality thus far reported in a series is 3 deaths in 31 tracheotomies with serum treatment, or a fatality of only 9.67 per cent. This is reported by Schroeder from the hospital in Altona.

If for each group of cases we estimate the number of deaths which would have occurred in the tracheotomized cases treated with serum on the assumption that the previous or simultaneous fatality in cases not treated with serum had obtained, we obtain the following result: The actual percentage of deaths in 510 tracheotomized cases treated with serum was 42.5. The percentage of fatality in these cases estimated on the basis of previous or simultaneous fatality in the same hospitals would be 64.5. There was therefore an apparent reduction in fatality by the serum treatment of 34.1 per cent. This difference between actual and estimated fatality is greater than is observed in any ordinary experience of variations in fatality during a series of years in the same hospital from tracheotomy in diphtheria.

I confess to some surprise that the analysis of the tracheotomized cases treated by serum should have yielded results so strikingly favorable to antitoxin treatment. When one considers that the benefits of serum treatment are most strikingly apparent when the treatment is begun early in the disease and become more and more doubtful after the third day, it would not have been a convincing argument against the treatment if these benefits were not conspicuously manifest in cases of diphtheria requiring tracheotomy, for, as has been explained, the great majority of these tracheotomized cases are already the subject of advanced laryngeal stenosis when the antitoxin is first injected. There are, however, not a few cases which begin apparently as laryngeal diphtheria (*croup d'emblée*), or in which the involvement of the larynx occurs within twenty-four or forty-eight hours after the onset of the attack. That careful observation would reveal in many of these apparently primary or early laryngeal diphtherias a latent or slightly manifested diphtheric angina I believe to be true.

It is interesting to note that in several reports the benefit of serum treatment has been much more evident in the operated cases than in those not operated on, although this is not the rule. Indeed Leichtenstern and Wendelstadt find in their series of 123 cases that the difference in favor of the serum in their non-operated cases was so small as to be without significance, whereas there was a difference in favor of the serum of 20.8 per cent. in their tracheotomized cases with and without serum treatment. They attribute, therefore, the entire benefit of the serum in their experience to its action in tracheotomized cases. Their experience, however, is exceptional, although in a measure approached by that of Ganghofner and of Van Nes. On the other hand, in Vierordt's experience the entire benefit of antitoxin seemed to be in the non-operated cases. As has been repeatedly explained, such diversities of experience with limited numbers of cases is to be expected, and the norm can be established only by observations of large numbers of cases in different places and at different times. This norm is that both operated and not operated cases are benefited by antitoxin, and that the difference in each class between serum fatality and fatality from other methods of treatment is a large one.

The fatality of intubated cases in Table II, treated with antitoxin, is 28.9 per cent., which is 10.9 per cent. less than the

fatality of tracheotomized cases. Before the introduction of the serum treatment a collective investigation was set on foot by the German Gesellschaft für Kinderheilkunde to determine the average fatality following intubation. In 1893 von Ranke reported to the Society that 1445 cases of diphtheria with laryngeal stenosis treated by intubation gave a fatality of 62.5 per cent. This result was interpreted in favor of intubation as opposed to tracheotomy. There is a difference of 33.6 per cent. between this percentage and that obtained from our 342 intubated cases treated with antitoxin. This difference is so great that, after making all possible allowance for differences in the series of cases entering into the two groups of statistics, it seems impossible to explain it otherwise than as a powerful additional support of the arguments already presented in support of the claims of antitoxin. Here certainly the objection that the cases treated by antitoxin were light ones cannot be made.

Table II enables us to compare the fatality of 250 intubated cases treated with antitoxin with the fatality estimated on the assumption that the previous or simultaneous fatality from intubation in the same hospital had obtained in the several groups. By this calculation we find the actual fatality to be 31.6 per cent., and the estimated fatality 62.4 per cent. In other words, there was an apparent reduction in the fatality of intubated cases of 49.5 per cent. as the result of the serum treatment.

However distrustful one may be of statistical evidence in therapeutics—and previous experience justifies much distrust—I fail to see on what credible assumption this striking reduction of fatality can be explained otherwise than as demonstrative of the specific curative power of antitoxin in diphtheria.

Lamentable for the victims but adapted to convince the skeptical were the experiences of Baginsky and Ganghofner during the periods of failure in the supply of serum. During the enforced two months' interruption of the serum treatment (August and September) in Baginsky's service there were 116 cases of laryngo-stenosis with a fatality of 62.2 per cent., as opposed to a fatality of 37.8 per cent. in the serum periods which preceded and followed the pause. The percentage of operations rose to 55.2 as opposed to 18.1 per cent. during the periods of serum treatment, and this without any change in the general character of the cases admitted. During the serum periods there were more intubations than tracheotomies, whereas during the pause there were 45 tracheotomies and 19 intubations, 13 of the latter requiring secondary tracheotomy. In Ganghofner's service the fatality of the operated cases rose from 13.6 per cent. to 68.9 per cent. during the interruption in the supply of serum.

There remain two points to be touched upon before dismissing the laryngeal stenoses. These are the substitution of intubation for tracheotomy in a larger and larger proportion of the laryngeal diphtherias requiring operative interference and treated by the serum, and the shortening of the period during which the tube or the tracheal canula is required to be kept in the air passage.

An agent which would arrest the progressive descent of the diphtheritic process from the larynx into the bronchi and hasten the disappearance of the obstructive exudate is just what was needed to make intubation the ideal operation for the relief of the great majority of cases of croup requiring operative interference. Such an agent we now possess in antitoxin for a large group of cases, and we are not surprised, therefore, to find that the employment of intubation, as a substitute for tracheotomy, has been greatly extended by the introduction of serum therapy.

Several writers give figures showing that serum therapy materially hastens the time when extubation or removal of the tracheal canula is permissible, but I have not attempted to collect these figures.

Of the 3127 not operated cases, including as already stated many cases of croup, 350 died, giving a fatality of 11.2 per cent. In V. Hirsch's statistics of diphtheria from von Bergmann's clinic for ten years the average fatality of not operated cases (1004) was 26 per cent., varying only from 25.9 per cent. during the first four years of the period to 27.3 per cent. during the last four years. There is, however, no general standard of fatality for cases of diphtheria not operated on. The variations are within very wide limits, as might be expected. Only a comparatively small number of the reports give separately the previous or simultaneous fatality of non-operated cases not treated with serum. I find in the reports the following data on this point. In Roux, Martin and Chaillou's report the previous fatality of non-operated cases averaged 33.9 per cent., the minimum being 32.1 per cent., and the maximum 47.3 per cent., as opposed to 12.8 per cent. under the serum treatment; in Baginsky's report the corresponding figures are 31.6 per cent. versus 10.9 per cent.; in Bokai's 34.5 per cent. versus 14 per cent.; in Ganghofner's 15.8 per cent. (the lowest in a series of years) versus 12 per cent.; in Van Nes 33 per cent., the average of ten years, with a minimum of 16 per cent. and a maximum of 41 per cent. versus 13.3 per cent.; in Leichtenstern and Wendelstadt's 15 per cent. versus 10.4 per cent.

Age is a factor of such prime importance in the prognosis of diphtheria that I have prepared the following table (Table III), in which the cases treated with serum collected from twenty-five reports are classified according to age. Unfortunately there is very little uniformity of system in the different reports in giving the results according to the ages of the patients, many of the reports simply stating the number of adults or the maximum age of the children or the number of cases under a certain age or the number between arbitrarily selected limits of age, etc., so that many of the reports were not used for the following table. In each space in the table the upper number is the total number of the cases belonging to the heading, and the lower number is the number of deaths among these cases.

The most frequently quoted percentages of fatality in diphtheria according to the age are those of Herz, and are as follows:

Under 1 year	80 per cent.
1–3 years	45 "
3–5 "	40 "
5–10 "	17 "
Over 10 years	17 "

TABLE III.

AGES OF PATIENTS TREATED WITH ANTITOXIN.

In each space the upper number is that of the cases and the lower that of the deaths.

REPORTER.	Total Cases.	Under 1 yr.	1-2 years.	2-3 years.	3-4 years.	4-5 years.	5-6 years.	6-7 years.	7-8 years.	8-9 years.	9-10 years.	10-12 years.	12-15 years.	Over 15 yrs.	REMARKS.
Kossel	117 13 (11 per ct.)	3 1	4 0	18 2	14 3	20 3	10 2	11 0	10 0	7 1	7 0	12 0	1 1		
Körte	121 40 (33.1 per ct.)														Of 15 infants under 2 years 8 recovered and 7 died.
Baginsky	525 83 (15.6 per ct.)	Under 2 years. 87 22		2-4 years. 146 25		4-6 years. 116 20		6-8 years. 79 9		8-10 years. 58 3		20 2	15 2		Of 4 cured cases the ages are not stated.
v. Widerhofer	100 24 (24 per ct.)	8 5	24 9	20 7	14 0	16 3	5 0	7 0	2 0	1 0		2 0	1 0		Deutsche Med. Wochenschrift, Jan. 10, 1895.
Schroeder	63 8 (12.7 per ct.)	Under 2 years. 6 3		2-10 years. 52 4								Over 10 years. 5 1			
Bokai	120 31 (25.5 per ct.)	1 1	22 10	22 7	24 4	18 3	13 1	6 1	7 3	2 0	1 0	4 1			69 cases were under 3 years of age.
Heim	27 6 (22 per ct.)		5 1	4 1	2 0	6 2	3 0	2 0	2 2			3 0			
Unterholzner	31 8 (25.8 per ct.)	2 1	9 5	7 2	3 0	2 0	1 0	2 0	2 0	8-13 years. 3 0					Of 21 under 4 years of age 13 recovered.
Börger	30 2 (6.6 per ct.)			1 0	2 0	1 0	1 1	3 0	2 0	2 0	2 0	3 1	2 0	11 0	16 cases were 10 years old or over.
Hager	25 1 (4 per ct.)	1 0	1 0	1 0	3 0	6 1	4 0		Over 6 years. 9 0						
Seiz	27 1 (3.6 per ct.)	1 0	4 0	2 1	6 0	4 0	4 0	1 0	2 0	3 0					Private practice.
Seitz	35 2 (5.7 per ct.)	Under 4 years. 18 2				4-6 years. 10		7-15 years. 7							One fatal case was 13 months, the other 18 months old; both with laryngeal diphtheria.
Reported in British Medical Journal, Feb. 2, 1895.	95 22 (23.2 per ct.)	4 2	9 3	6 1	12 1	10 3	5-10 years. 23 9					10-15 years. 15 2		16 1	
Goodall	72 14 (19.4 per ct.)	4 1	10 2	7 1	9 3	10 5	22 2					10 0			British Med. Jour., Jan. 12, 1895. These are the ages of the cases previously reported by Washbourn, Goodall and Card.
Hall	11 3 (27.3 per ct.)		1 0					1 1		1 1		1 0	2 1	5 0	
Epidemic in Trieste. Hospital Cases.	105 27 (25.7 per ct.)	9 5	12 5	12 6	15 3	16 5	13 1	7 0	6 1	4 0	3 1	6 0		3 0	
Epidemic in Trieste. Cases in private practice.	72 5 (6.9 per ct.)		2 0	3 2	8 1	11 1	12 0	5 0	1 0	7 1	2 0	3 0	7 0	1 0	10 cured cases are not accounted for in this series.
Blumenfeld	50 2 (40 per ct.		6 1	5 0		5 0	5 0	14 0	5 1			10-13 years. 9 0		1 0	Private practice.
Schaewen	15 0		1 0			1 0	2 0		3 0		3 0	2 0	2 0	1 0	Private practice.
Rapmund	100 7 (7 per ct.)	1 0	6 1	12 2	3-5 years. 22 1	5-10 years. 43 3						10-20 yrs. 15 0	Over 20 yrs. 1 0		Private practice. 14 cases were under treatment at time of report.
v. Muralt	58 2 (3.4 per ct.)	1-3 years. 21 1				Over 3 years. 37 1									The latter fatal case was of a tracheotomized child 4 years old admitted on the 6th day of the disease; the former case was of an infant two years old with syphilis, measles and pneumonia.
Codd and Whitehouse	11 4 (36.4 per ct)	1 0		1 1		1 1	1 0	1 0		2 0	2 0		1 1	1 1	The fatal case in an adult was of a woman 39 years old admitted in a state of collapse on the 8th day of the disease and dying in 24 hours
Winkfield	22 4 (18.2 per ct.)		1 1	2 1		4 0	2 1	3 1	2 0	3 0		2 0	1 0	2 0	
Van Nes	52 12 (23 per ct.)		1 0	7 4	4 2	9 4	8 0	7 0	6 1	3 1	2 0	5 0			
Leichtenstern and Wendelstadt.	123 25 (20.3 per ct.)	0-2 years. 36 11		2-4 years. 32 6		Over 4 years. 61 8									Of 17 tracheotomized infants less than 2 years old, 9 died: of 13 unoperated patients less than 2 years old, 2 died; of 11 tracheotomized patients between 2 and 4 years, 4 died; of 21 unoperated cases between 2 and 4 years, 2 died.

As the cases in the preceding table were not classified according to the ages by a uniform plan in the different reports they cannot all be summarized in a single table, but the chief results can be presented as follows:

14 Reports.	Total.	0-2 yrs.	2-4 yrs.	4-6 yrs.	6-8 yrs.	8-10 yrs.	10-12 yrs.	12-15 yrs.	Over 15 yrs.	Undetermined.
Cases	1234	187	327	297	176	114	63	32	24	(14)
Deaths	215	60	70	48	19	8	4	5	1	(0)
Percentages	17.4	32.1	21.4	16.2	10.8	7	6.63	1.6	4.1	(0)

In the following table the cases under 4 years are from 20 reports containing 1630 cases (fatality 17.6%) and those over 4 are from 17 reports containing 1451 cases (fatality 17.4%).

	0-2 years.	2-4 years.	4-10 years.	10-15 years.	Over 15 years.
Cases	263	411	681	129	40
Deaths	86	84	95	11	2
Percentages	32.7	20.4	13.9	8.5	5

The following table gives the results for each year up to 5 and over 5 years.

18 Reports.	Total.	Under 1 year.	1-2 years.	2-3 years.	3-4 years.	4-5 years.	Over 5 years.	Undetermined.
Cases	982	34	112	118	116	140	452	(10)
Deaths	179	16	37	36	17	31	42	(0)
Percentages	18.2	47.1	33	30.5	14.7	22.1	9.3	(0)

The table furthermore shows under one year 35 *cases with* 16 *deaths or* 45.7%; *under* 2 *years* 291 *cases with* 97 *deaths, or* 33.3%; *under* 3 *years* 304 *cases with* 93 *deaths or* 30.6%, *and under* 4 *years* 692 *cases with* 122 *deaths or* 17.6% (*each of these four groups of cases being from a total number of cases in the first group of* 1080 *cases, in the second group of* 1914 *cases, in the third group of* 1140 *cases and in the fourth group of* 1665 *cases, the average fatality for the whole number of cases being* 17.3%.)

The percentages of fatality in V. Hirsch's statistics of 2658 cases from the surgical clinic in Berlin for 10 years and 7 months (ending July 31, 1894), according to age are:

Under 1 year.....88.3 per cent.
1–2 years.....82.5 "
3–4 " .....63.9 "
4–5 " ..... 56.6 "
5–6 " .....46.9 "
6–7 " .....43.7 "
7–8 " .....36.1 "
8–9 " .....28.1 "
9–10 " .....31.1 "
10–11 " .....21.2 "
11–12 " .....20.9 "
12–13 " .....18.5 "
13–14 " .....16.7 "
14–15 " .....15. "
15–16 " .....12.5 "
Adults (72 cases).....11.1 "

Baginsky gives the following percentages from his service in the Kaiser- und Kaiserin-Friedrich Children's Hospital in Berlin as the mean of the four years 1890 to 1893 inclusive:

Under 2 years .....60.2 per cent.
2–4 years .....51.2 "
4–6 " .....38. "
6–8 " .....28.9 "
8–10 " .....24.5 "
10–12 " .....28.8 "
12–14 " .....18.5 "

Baginsky's results in Table III may be compared with this last list of percentages, otherwise I do not consider that these statistics of Herz, Hirsch and Baginsky furnish any certain standard of comparison for the percentages of fatality derived from Table III. I have cited them, however, in the absence of any such standard to show in a general way that these latter percentages indicate a low fatality according to age. The contrast between a fatality percentage of 33.3 for cases of diphtheria under two years of age treated with serum, and that of 60 to over 80 for cases of the same age not so treated is a striking one, even if a large allowance be made for differences in the characters of the cases in the two groups.

We come now to the consideration of the influence upon the fatality of the length of the interval between the onset of diphtheria and the first injection of antitoxin. In experiments upon animals this factor is decisive in determining the result.

It is the factor which Behring from the first has put in the foreground. His claim is that no death will occur from diphtheria if antitoxin is injected in sufficient dose at the beginning of the disease, and that the fatality will fall under 5 per cent. if the treatment in proper manner is begun before the third day of the disease.

Of course the only significance of this great emphasis upon the importance of early treatment is as an expression of the fact that cure is rendered more difficult the larger the number of the diphtheria bacilli, the greater the amount and intensity of their toxins, the greater the damage already inflicted by the bacilli and their toxins, and the more serious the complications and secondary infections. There is, however, no absolute parity between the length of time the disease has lasted before beginning treatment and the increase of these dangers. One case may become desperate within forty-eight hours after the onset, and another may present no grave symptoms after a week's duration. The virulence, the number and the

microbic associations of the infecting bacilli, and especially the local and general susceptibilities of the patient, are factors no less important than the single factor of time in influencing the issue.

The individual peculiarities of each case must be considered. If all is judged according to one simple uniform standard—antitoxin cures the case or it does not cure the case—and it must be confessed this is all which seems to be in the minds of many, then the practitioner will not come to any clear conception of the wonderful powers of the healing serum. The sins of some observers in this matter seem incredible. They lump together indiscriminately all of their cases, including those complicated with measles, scarlet fever, tuberculosis and other diseases, the mixed infections, the anginas, the croups, the advanced and the early cases, the true and the false diphtherias, the infants and the adults, and throw them into the scale to be weighed for or against antitoxin. An unsuccessful case is put down to the discredit of antitoxin without reference to its peculiarities. On the basis of experience in treating a dozen cases, the writer boldly attacks results established by the careful observation of hundreds of cases. It is true we need these brute figures for comparison with former fatality statistics of diphtheria, and they have served to demonstrate the curative efficacy of antitoxin, but reports of personal experience with the serum treatment should at least contain the data for an intelligent analysis of the cases treated. Such an analysis is requisite in order to reveal the full scope and capabilities of the new treatment. We have already seen that the study of the cases with reference to laryngeal involvement has brought to light evidence in favor of the serum treatment more convincing than that derived from the gross statistics of all cases treated, and evidence of a kind which meets many of the objections which have been urged against the interpretation of the gross statistics as demonstrative of the efficacy of antitoxin. We shall now see that the analysis of the cases according to the day of the disease on which the serum treatment is begun almost, if not completely, substantiates Behring's original claims, astounding as they seemed to be.

There is, of course, in many cases considerable uncertainty as to the exact duration of the disease at the time when the patient is first seen by the physician. The statements of parents or of those in charge of the children are often the only evidence on this point which can be obtained. Satisfactory information will be particularly difficult to obtain in the class of patients in the diphtheria wards of hospitals, these patients being chiefly the children of laborers. We are also to consider that a diphtheric affection of the throat may exist without such manifest disturbance as to attract even intelligent observation, or it may be mistaken for a simple sore throat. A tabulation of cases of diphtheria according to the day of beginning treatment will be, therefore, only of relative value, but we can fairly assume that the duration of the disease will very rarely, if ever, be shorter, but often longer, than that stated.

In the excellent reports on antitoxin treatment from the Paris hospitals, the cases are not analyzed according to the day of beginning treatment, as Roux, whose scheme of classification has been followed by most other French writers, stated in his original article that it was practically impossible to obtain trustworthy statements on this point from parents of the children. Most of the reports, therefore, which enter into Table IV are from German and English sources.

The statements as to the day of the disease are entirely from information obtained from parents and others, and are not estimates on the part of the physician, although in several instances the reporter says that the condition of the patient plainly indicated a longer duration of the disease than that assigned by the parents and put down in the report. It will be observed that not all of the reports in the table fit into any one system of classification, and therefore not all can be summarized in a single table. In each space the higher number is the total number of cases belonging to the heading, and the lower is the corresponding number of deaths.

As is well known, the fatality from diphtheria by any approved method of treatment is smaller the earlier in the disease the treatment is begun. This is clearly shown in the following table from the statistics of V. Hirsch of the cases treated in the surgical clinic in Berlin for ten years preceding August, 1894, and of course before the employment of antitoxin. The results are according to the day of the disease on which treatment was begun.

	First Day.	Second Day.	Third Day.	Fourth Day.
Cases, . . .	241	405	323	416
Deaths, . . .	44	92	124	223
Percentages, .	18.3	22.7	38.1	53.6

	Fifth Day.	Sixth Day.	Seventh Day.	Eighth Day.
Cases, . . .	203	525	506	239
Deaths, . . .	136	219	367	191
Percentages, .	67	67.4	72.5	81.6

The preceding table is not intended to serve as a standard of comparison for my tables giving the results of cases treated by antitoxin, as the classes of cases in the two groups are not comparable.

Philip* has reported from Baginsky's service the results of treatment, before the use of antitoxin, begun in the earliest stages of diphtheria, the patients being brothers and sisters of children with diphtheria who were examined for Löffler bacilli, so that opportunity was given for recognition of the disease at its onset. The fatality was 10.5 per cent. lower in these cases recognized and treated early than in the others. The fatality of the cases treated by Baginsky with serum during the first three days of the disease was 32.2 per cent. lower than the preceding average fatality of cases not treated with serum. Plainly some more potent healing factor than merely that of early treatment was present. The only difference in the methods of treatment of the two groups of cases was the use of antitoxin in the one and its absence in the other.

* Philip: Arch. f. Kinderheilk., Bd. XVI.

TABLE IV.

FATALITY ACCORDING TO THE DAY OF DISEASE UPON WHICH ANTITOXIN IS INJECTED.

(In each space the higher number is the total number of cases treated on the corresponding day, and the lower number is that of the deaths.)

REPORTER.	Total number of Cases Treated.	1st Day.	2nd Day.	3rd Day.	4th Day.	5th Day.	6th Day.	After 6th Day.	Undetermined.	REMARKS.
Kossel	117 13 (11.1 per ct.)	14 0	30 1	29 0	9 1	11 2	6 3	12 5	6 1	Fatality for first three days was 1 4 per cent.
Körte	121 40 (33.1 per ct.)									Of 37 severe and moderately severe cases injected during the first three days 8 died (21.6 per cent). The results following injection begun after the third day were less favorable.
Baginsky	525 83 (15.6 per ct.)	111 3	134 14	92 13	52 12	39 14	13 4	29 12	55 11	All of the three fatal cases of the first day were far advanced on admission, therefore the statements of the parents as to the date of beginning of the disease were probably erroneous (Baginsky). Fatality for first three days was 8.9 per cent.
v. Mering	74 4 (5 per ct.)									Treatment begun on 1st or 2nd day in nearly all cases.
v. Noorden	81 19 (23 per ct.)									Treatment begun on the 3rd or later day in nearly all cases.
Schroeder	63 8 (12.7 per ct.)	1st & 2nd Day. 23 1		3rd & 4th Day. 27 3		After 4th Day. 13 4				
Vierordt	55 8 (14.6 per ct.)	3 0	14 2	17 2	9 0	7 3	1 0	4 1		
Rumpf	26 2 (8 per ct.)		18 1	3 1	After 3rd Day. 5 0					4 cases were still under treatment at date of the report.
Ganghofner	110 14 (12.7 per ct.)	3 0	30 2	35 3	18 4	9 3	2 0	13 2		
Heim	27 6 (22 per ct.)		9 0	2 1	7 1	3 1	1 0	5 3		
Börger	30 2 (6.6 per ct.)	3 0	13 0	9 0		3 1	1 0	1 1		
Hager	25 1 (4 per ct.)	14 1	5 0	4 0	1 0			1 0		Private practice. The single fatal case died of complications after cessation of the diphtheria.
Kuntzen	25 3 (12 per ct.)	3 0	6 0	7 1	2 0	2 0	1 1	4 1		
Schmidt	14 3 (21.4 per ct.)									The three fatal cases were not treated until after the disease had lasted for 8 to 14 days. Private practice.
Seitz	35 2 (5.7 per ct.)		10	12	9	After 4th Day.				The two deaths were in infants 1½ years and 13 months old with advanced laryngeal diphtheria on day of admission, presumably therefore treated after 2nd or 3rd day, although this is not stated.
Hall	11 3 (27.3 per ct.)	2 0	4 0	4 2		1 1				
Epidemic in Trieste Hospital cases	105 27 (25.7 per ct.)	6 0	30 5	29 9	20 5	11 4	7 3	2 1		
Epidemic in Trieste Cases in private prartice	72 5 (6.9 per ct.)	14 0	27 2	18 1	8 2	2 0	2 0	1 0		
Witthauer	36 5 (14 per ct.)	4 0	8 2	4 1	6 0	3 0		11 2		
Blumenfeld	50 2 (4 per ct.)	1st & 2nd Day. 40 0		3rd & 4th Day. 8 1		2 1				Of the 2 fatal cases, in one the treatment began on the 4th and in the other on the 5th day. Private practice.
Rapmund	100 7 (7 per ct.)	39 2	34	15 3	5	3 2	1	3		The deaths are given for the 1st and 2nd, the 3rd and 4th and the 5th, 6th and after 6th day respectively.
Schaewen	15 0	6 0	3 0			1 0			5 0	Of the 5 undetermined cases the statement is that they had been ill several days before the injection.
Risel	114 9 (7.9 per ct.)		78 4	21 4	4 0	4 0	5 1		2 0	89 of these cases were treated at their homes, and 25 in hospital. They were mostly children.
v. Muralt	58 2 (3.4 per ct.)	11 0	18 0	17 0	After 3rd Day 12 2					
Codd and Whitehouse	11 4 (36.4 per ct.)	1 0	2 0	5 2		2 1		1 1		
Winkfield	22 4 (18.2 per ct.)		8 2	7 1	4 1	2 0		1 0		Of the 2 fatal cases in which it is stated the injection was made on the 2nd day, in one there were on admission advanced laryngeal and nasal diphtheria with glandular swellings, and in the other thick membranes in the throat, nasal discharge and glandular swellings.
Howard	40 3 (7.5 per ct.)	24 0	7 0	2 0	2 1	3 0	2 2			Private practice.
Van Nes	52 12 (23 per ct.)	2 1	13 1	10 1	7 2	8 3		12 4		No details given of fatal case said to be treated on 1st day of the disease, but it is noted that the determination of the day was very uncertain in the class of patients (children of laborers) admitted.
Kurth	97 10 (10.3 per ct.)	12 0	35 2	16 1	19 3	5 1	3 1	7 2		Of the 2 fatal cases in which it is stated the injection began on the 2nd day, one was admitted with croup and died 18 hours afterward; the other died a month after disappearance of the local diphtheria with albuminuria and broncho-pneumonia.

The following table is the summary of the 19 reports of the preceding table in which the number of the cases with the results corresponding to the disease on which antitoxin treatment was begun is given for each day up to and after the 6th day.

19 Reports.	Total.	1st Day.	2nd Day.	3rd Day.	4th Day.	5th Day.	6th Day.	After 6th Day.	Undetermined.
Cases	1489	322	456	311	168	116	44	104	(68)
Deaths	212	5	37	42	32	34	15	35	(12)
Percentages	14.2	2.2	8.1	13.5	19	29.3	34.1	33.7	(17.6)

Including with the preceding 19 *reports those of Schroeder, Blumenfeld and Rapmund, we have the following table which gives the results of antitoxin treatment begun on the* 1st *and* 2nd, *on the* 3rd *and* 4th, *and after the* 4th *day.*

22 Reports.	Total.	1st and 2nd Day.	3rd and 4th Day.	After 4th Day.	Undetermined.
Cases	1702	814	534	286	(68)
Deaths	229	45	81	91	(12)
Percentages	13.5	5.5	15.2	31.8	(17.6)

It may also be computed from the table that of 1729 *cases of diphtheria with a fatality of* 14.9%, 1115 *cases treated with antitoxin during the first three days of the disease yielded a fatality of* 8.5%, *whereas* 546 *cases in which antitoxin was first injected after the third day of the disease yielded a fatality of* 27.8%. *Of* 232 *cases in which treatment was begun on the first day* 5 (2.15%) *died; of* 492 *cases in which treatment was begun on the second day,* 38 (7.7%) *died; of* 331 *cases in which treatment was begun on the third day,* 43 (13%) *died.*

Kohts, an opponent of the serum treatment, at the recent Congress for Internal Medicine in Munich, claims for his method of local treatment no deaths among cases treated on the first day of the disease. For later days his results are much higher than those in the serum statistics. The percentages of deaths according to the day of beginning his treatment, as given by Kohts, without a statement of the number of cases treated, are as follows: 1st day, 0; 2nd day, 20 per cent.; 3rd day, 47 per cent.; 4th day, 55 per cent.

Table IV shows that out of 232 cases in which it is alleged that antitoxin was injected on the first day of the disease, 5 died. As a matter of fact, however, the assumed duration of the disease in each of these fatal cases is doubtful, as it rests solely on the statements of parents or those who cared for the children, and is apparently contradicted in at least the three cases concerning which any details are given by the condition of the patient on admission. Baginsky's three cases (Nos. 311, 479 and 511 of his tables) when admitted were far advanced in the disease, with extensive membranous exudates, cyanosis and very bad general condition. Hager's case may more readily be accepted, as it occurred in private practice, but here the patient died after disappearance of the diphtheria from complications, whether or not referable to the diphtheria is not stated.

Of the fifth fatal case reported by Van Nes no details are given in such form that the case can be identified from his description, but he himself places little reliance upon the alleged duration of the disease in the class of patients admitted to the hospital, these being the children of laborers.

I am not aware of the report of any fatal case of diphtheria properly treated by antitoxin within the first 24 hours after the beginning of the disease, in which the duration was positively determined, still as I have not read every article which has been published on the subject it is possible that such a case may have been reported. There are, however, many such cases of prompt recovery reported as that quoted from Hall in Table IV.

It is noteworthy that the percentage of deaths in 814 cases in which treatment was begun before the third day of the disease is only 5.5. If the doubtful deaths attributed to the first day be excluded, the percentage actually falls a trifle short of 5. If we furthermore make allowance for the fact that the assigned duration of the disease can scarcely be shorter, but may readily be longer than the actual duration, then our tabulation of 1702 cases of diphtheria according to the day of beginning treatment verifies Behring's original prediction. I do not, however, consider that it is justifiable from so small a number of cases and from material of the kind composing our table to draw any definite conclusions as to the exact percentages of deaths according to the date of beginning treatment.

According to the table the percentage of deaths in cases in which the serum treatment is begun on the 3rd and 4th days of the disease is nearly three times greater than that in cases treated on the 1st and 2nd day, and the percentage after the 3rd day is 3¼ times greater than that of cases treated within the first three days.

We are of course not to infer from these results that antitoxin may not be beneficial when administered after the 3rd or 4th day of the disease. There are cases which are still mild after this duration, but which subsequently become serious, and even in desperate cases antitoxin holds out some hope of cure.

It is apparent that the largest proportion of cures by antitoxin are to be expected from private practice among those who call the physician in at an early stage of the disease. While a similar statement may be made concerning any other suitable method of treatment, it is not, I believe, true in the same measure as for the serum treatment.

The main purpose of this article has been the study of the evidence thus far published concerning the curative power of antitoxin in diphtheria. I do not propose to consider the practical points relating to the employment of antitoxin, nor to consider in detail the specific effects of injection of the healing serum. There has been much diversity of opinion as to these effects, and I shall present briefly the principal points which seem to me to be established.

Most writers approve of the continuance of such measures of local and general treatment as have hitherto been found to be useful, but recommend the avoidance of all irritating and caustic local applications.

The injection of the serum may be followed in a few hours by local pain, swelling and redness, but there is no danger of abscess formation if the serum is uncontaminated and proper antiseptic precautions are taken. In over 3000 injections Martin observed the formation of an abscess only three times.

In twenty-four to forty-eight hours after the injection the general condition of the patient is remarkably improved in the great majority of those patients who are in a condition to be benefited at all by antitoxin. This general improvement is accompanied by a fall of temperature, which may be a critical fall, especially if the disease is not far advanced;

often it is a fall by lysis. Some hold that there may be a temporary rise of temperature as an immediate effect of the injection. Accompanying the fall of temperature is improvement of the pulse as to frequency and tension, but the heart's action may for some time, even into the period of convalescence, remain weak.

In the favorable cases the local diphtheritic process is arrested, usually within the first twenty-four hours after the injection. Membrane may appear upon spots previously inflamed and invaded by the bacilli, but otherwise there is no extension of the membrane in the majority of the cases which are benefited. The area covered by membrane becomes sharply demarcated and the swelling of adjacent mucous membrane disappears. The membrane may disappear by rapid separation or by gradual softening. Sometimes it persists for several days after disappearance of all other local disturbance. Large membranous casts are coughed up from the larynx, trachea and bronchi under the serum treatment more frequently than under former methods. The rapid separation of the membrane in the lower air passages may cause sudden increase of stenotic symptoms. Nasal discharge is lessened. The swelling of the glands in the neck and the surrounding œdema disappear, so far as these are not referable to secondary infections.

The most uncertainty prevails as to the influence of antitoxin in preventing the three most important complications or sequelæ of diphtheria, nephritis, heart failure and paralysis. The weight of evidence is that genuine nephritis is far less common in cases treated by antitoxin sufficiently early than under other methods of treatment, but it is questionable whether albuminuria is less common, although it is considered to be by Kossel, Roux and others. If there is an albuminuria in any way directly referable to the injection of the serum, and this is by no means established, it is simple albuminuria with perhaps a few narrow hyaline casts but without evidence of any serious damage to the kidney. Peptonuria, it is claimed by Hecker, is an effect of the serum, but it is without clinical significance. Albuminuria is such an extremely common symptom of diphtheria that it must be very difficult to determine that it can be referred to the serum in any case.

Many writers emphasize especially the favorable influence of antitoxin upon the heart, but there are some who have observed that with decided improvement in all other symptoms the force of the heart may still remain weak and occasion anxiety. Baginsky's experience is that the minor disturbances of the cardiac action are not less frequent in cases treated with serum, they appear to be even more frequent as a larger number of cases survive, but that actual death from heart failure is far less common in the serum cases than in others.

Post-diphtheric paralyses may occur in cases treated with serum as early as the second or third day of the disease. Whether they occur in cases treated within the first twenty-four hours is not certain. According to some, paralysis is even more common in the serum cases than under former methods of treatment. This is doubtful, but if true, it may be attributed to the survival of a larger proportion of cases.

It is apparent from what has been said that antitoxin is most strikingly beneficial in progressive fibrinous diphtheria and especially in the prevention and cure of laryngeal diphtheria. In septic diphtheria the serum treatment is of little avail.

Antitoxic serum may produce unpleasant effects, but these do not involve danger to the patient. They are in all probability referable to the serum as such and not to the healing, so-called antitoxic, substance contained in the serum. The most common undesired effect is some form of exanthem, usually erythema and urticaria, sometimes an eruption like measles or scarlatinal rash. The same exanthems have been observed by Bertin after the injection of ordinary serum of the horse, and by Richardière after injection of Marmorek's anti-streptococcus serum.

The serum from some horses is more likely to cause these exanthems than that from others, and there may be individual idiosyncrasies favoring their occurrence. Some writers report the occurrence of an exanthem in not more than five per cent. of their cases, others have observed them in over fifty per cent. of the cases treated with serum. They may be localized in the neighborhood of the seat of injection or extend from that over the greater part of the body, or make their first appearance at a distance from the point of injection. Often without noticeable fever they may be accompanied by considerable elevation of temperature and by pain and swelling in the joints. A rarer but more severe form of serum exanthem resembles erythema multiforme, and when this is accompanied, as it may be, by high fever, and severe pain in the bones and joints with swelling of the joints, the condition of the patient may really seem serious, but these patients recover. Some have attributed a petechial eruption to injection of the serum, but this may occur in diphtheria without serum treatment.

These occasional untoward effects of the healing serum are annoying, but, being unattended with danger to life and without serious consequences, they do not contraindicate the use of the serum.

There have been a few cases reported in which the writers, without any satisfactory evidence whatever, have referred the death of the patient to the use of the serum. The essential harmlessness of the serum has been demonstrated by over a hundred thousand injections,* and if future investigations should show that through some idiosyncrasy on the part of the patient death ever is attributable to the injection of the serum, this would probably count for about as much as the rare deaths from the use of ether or chloroform.

I shall leave untouched the question of the immunizing properties of antitoxin.

The principal conclusion which I would draw from this paper is that our study of the results of the treatment of over 7000 cases of diphtheria by antitoxin demonstrates beyond all reasonable doubt that anti-diphtheric serum is a specific cura-

* This would seem to be at least a moderate estimate, as writing November 20, 1894, Behring says that there had been up to that date certainly over 40,000 injections (Das neue Diphtheriemittel, von Dr. Behring, Berlin, 1894, p. 25).

tive agent for diphtheria, surpassing in its efficacy all other known methods of treatment for this disease. It is the duty of the physician to use it.

The later reports show in general a decided improvement in the results of the treatment over the earlier ones, and there is every reason to believe that the results of the second year's employment of the new treatment will make a much more favorable showing than those of the first year. We shall come to a clearer understanding of the mode of action of the healing serum. Improvements in the methods of preparation and preservation of the serum, and possibly the separation of the healing substance, at least from other ingredients which produce the undesired effects, may be expected.

The discovery of the healing serum is entirely the result of laboratory work. It is an outcome of the studies of immunity. In no sense was the discovery an accidental one. Every step leading to it can be traced, and every step was taken with a definite purpose and to solve a definite problem.

These studies and the resulting discoveries mark an epoch in the history of medicine. It should be forcibly brought home to those whose philozoic sentiments outweigh sentiments of true philanthropy, that these discoveries which have led to the saving of untold thousands of human lives have been gained by the sacrifice of the lives of thousands of animals, and by no possibility could have been made without experimentation upon animals.

A MORE RADICAL METHOD OF PERFORMING HYSTERECTOMY FOR CANCER OF THE UTERUS.

By J. G. Clark, M. D., *Resident Gynecologist.*

The onset of carcinoma of the uterus is so insidious, and its early stage gives rise to so few disagreeable subjective symptoms, that finally, when the patient is forced by repeated hemorrhages, which usually first alarm her, to consult a physician, the disease has passed beyond the possibility of a radical operation for its cure.

The route of upward extension is almost invariably by the broad ligaments; and on account of the close attachment of the lower portion of the ligament to the cervix, the progress is rapid through the intraligamentary lymphatics, and if not checked in the early stage is soon beyond the limits of any operation.

The downward growth on the vaginal walls and the metastasis from this point is often so very extensive that it also cannot be removed by the usual methods.

A casual review of the literature of the operative treatment of carcinoma is sufficient to convince one of the inadequacy of any method of treatment; but as the operative method is the only one which offers any chance of cure or benefit at present, it should be employed in all cases where the disease has not passed beyond the palliative effect of hysterectomy.

If the broad ligaments are densely infiltrated and the cervix deeply excavated, any form of radical operation is out of the question, as there is no possibility of even alleviating the symptoms.

If on the other hand the cervix is extensively ulcerated and the broad ligaments only slightly involved, the prognosis is favorable at least for the euthanasic effect of hysterectomy, and in a certain proportion of cases the disease can be removed completely even by the ordinary methods of hysterectomy.

During the last six months the clinical courses of three inoperable cases admitted to the gynecological wards of the Johns Hopkins Hospital have been closely followed, and in reviewing the histories of these cases in conjunction with the autopsy notes, we are more than ever convinced that any measure which offers the slightest prospect of mitigating the agonizing pain and relieving the symptoms caused by pressure of the growth upon the rectum and ureters should urgently be advised.

Death in cases which are not operated upon is usually caused by obstruction of the ureters (uræmia), peritonitis, or toxæmia from septic absorption.

The involvement of the ureters is usually late, but many weeks before this complication arises the sacral plexus may be pressed upon in one or both sides of the pelvis by the carcinomatous masses wedged into the inferior strait, and the patient suffer the most agonizing sacral and sciatic pain.

One of the three cases just referred to was of this type. The patient was admitted to the hospital six months before her death, and throughout the remaining days of her life was not free from pain a single hour, even under the influence of large doses of morphine.

The autopsy revealed a dense board-like infiltration of the broad ligaments which extended out to the pelvic wall, involving the sacral plexus at its points of egress from the sacrum. In this case had the uterus and broad ligaments been totally extirpated, even six months before the patient was admitted, the progress of the disease would probably not have been arrested, but she would have been spared the frightful agony of the last six months of her life by the relief of the pressure on the nerves. The left ureter in this case was completely blocked, and in addition to the pressure pains which she suffered there was present a partial uræmic toxæmia for three months before death which caused constant nausea and considerable vomiting.

The second patient, a mulatto woman, was admitted three months before death with a deep crater-like excavation of the cervix and dense induration of the broad ligaments. She suffered intense pain, which was only partially controlled by morphine, and at last died of peritonitis from perforation of the lateral wall of the uterus into the peritoneal cavity. Her abdomen became intensely tympanitic, and for five days before death her temperature ran as high as 105° to 107° F.

In the third case death resulted from uræmia, both ureters being blocked, and in addition there was a pyelonephrosis and ureteritis on one side. For 72 hours before death there was total suppression of urine. In these cases we have exemplified the three usual terminations of carcinoma which are not subjected to operation: (1) asthenia and uræmia from toxic absorption; (2) peritonitis from perforation of the uterus, and (3) uræmia, and pyelonephrosis from septic infection. These three cases also give us a vivid composite picture of the frightful suffering which these unfortunate women experienced.

The offensive discharge from the necrotic tissue is another excessively disagreeable symptom which invariably appears as soon as the ulcerative process is well under way, and can only be stopped by a complete removal of the carcinomatous tissue. This is of itself a justifiable indication for operation, as the discharge is always checked for some time, and frequently does not reappear even though the disease continues to extend.

It is Dr. Kelly's rule to advise hysterectomy in all cases which have not passed beyond the limit of the palliative effect of the operation, even though there is no possibility of a cure, simply for the relief of the inevitable symptoms which must arise if the uterus is not removed.

For the radical cure of cancer of the uterus the same surgical rule obtains as in cancer of other regions, viz. total extirpation of the primary focus and as extensive areas of adjacent tissue as possible to insure the complete eradication of the disease.

It cannot be gainsaid that it is better to have a local recurrence and ultimate death from metastasis following the removal of the uterus, with a decided amelioration of the usual distressing symptoms, than to have these symptoms increasing in their severity until death without operation.

The faults common to all methods of removing the uterus are (1) the broad ligaments are cut too close to the uterus, and (2) too small portions of the vagina are removed. (Fig. III.)

In at least 95 per cent. of cases where there is upward extension of the disease it is through the lymphatics of the broad ligaments. The local recurrence which we so often see on the margins of the vaginal incision also demonstrates very clearly the fact that usually too little of the vagina is removed.

In carcinoma of the fundus the extension is invariably through the broad ligaments, and any operation which removes a considerable portion of these structures offers the greatest hope of a permanent cure.

The usual methods of performing hysterectomy have been extremely unsatisfactory to every gynecologist, for the reason that only a small portion of the broad ligaments is removed and the remainder usually conceals nests of epithelial cells which fall outside the limit of the knife. The same may be said of the vagina. The results of the pathological examination of the uteri removed by hysterectomy in the Johns Hopkins Hospital not only definitely sustain this clinical observation, but also point strongly to the necessity of a more radical method than yet proposed.

Of the last 20 cases, the specimens have been submitted to a most careful pathological examination, which has shown that in 15 cases the carcinomatous process had passed beyond the limit of operation; in one case the result was doubtful, and in only four cases could it be definitely said that all of the disease had been completely removed.*

No stronger argument than this can be advanced for a more radical operation.

In at least five instances where the extension had occurred along either one or both broad ligaments, the carcinoma could not have passed more than a few millimeters beyond the limit of operation, as the epithelial cells were very sparse and were only barely perceptible in the margins of the incision.

In other cases there was no involvement of the broad ligament, but too little of the vaginal wall had been excised.

In comparing Fig. III of a uterus removed by vaginal hysterectomy and Fig. IV of the specimen from Case II which was removed by the method which I shall describe, it will be seen that none of the broad ligament or the vaginal wall is removed with the former, while with the latter there is a large portion of the broad ligaments and a considerable cuff of vagina.

The great danger of cutting or ligating the ureters in the past (Fig. II) has prevented a wide excision of the broad ligaments, but now that Dr. Kelly has entirely removed this danger by introducing bougies into the ureters in all operations where they may be involved, we can turn our attention with greater confidence to the more extensive extirpation of the tissues adjacent to the uterus.

The value of this procedure has been frequently demonstrated in Dr. Kelly's clinic, and if generally adopted will no doubt save many lives which are lost from cutting or tying the ureters.

After laying a plan before Dr. Kelly for the more complete extirpation of the uterus, the broad ligaments and a portion of the vagina, and receiving his cordial endorsement and encouragement, I was granted the opportunity in April, 1895, to put into effect the principles embodied in the proposed operation. There are three essential steps in this operation which differ from those now employed: 1st, the introduction of the bougies; 2d, the ligation of the upper portions of the broad ligaments, including the round ligaments and ovarian arteries, cutting them close to the pelvic walls, opening the two layers and dissecting the uterine artery out to its origin and ligating before excising any tissue, and 3d, the excision of a much larger portion of the vagina than usual.

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* In a forthcoming article by Dr. Russell upon the clinical course of cases subsequent to hysterectomy for carcinoma in the Johns Hopkins Hospital, it will appear that there is a greater percentage of permanent cures than the pathological examination of these 20 cases would seem to indicate. From the opening of the hospital in 1889 to August 1894, 48 hysterectomies were performed; of this number 41 were vaginal, 4 abdominal and 3 combined vaginal and abdominal. The results of these operations are as follows: 5 died from the primary effect of the operation, 17 died subsequently from extension of the disease, 6 have not been heard from, and 20 *are still living*. Assuming that of the 6 not yet heard from 3 are living and 3 dead, there are 48 per cent of these cases still living, certainly a very gratifying result, as it has now been nearly a year since the last of this series of cases was operated upon.

By carefully ligating the artery in this way, and introducing the bougies, we eliminate the dangers of hemorrhage and of injury to the ureters, and are enabled to extirpate the uterus, its broad ligaments, and the upper portion of the vagina *en masse*.

The value of excising the carcinomatous tissue in one piece is dwelt upon with much stress by Dr. Halsted in the description of his operation for cancer of the breast, by means of which he has reduced the ratio of local recurrence from 50 to 20 per cent.* The same rule must hold good here.

He says "the suspected tissue should be removed in one piece: (1) lest the wound become infected by the division of tissue invaded by the disease or of lymphatic vessels containing cancer cells, and (2) because shreds or pieces of cancerous tissue might readily be overlooked in a piecemeal extirpation."

The principal reason for the careful dissection and exposure of the uterine artery is that one can tie it well out in its course and then, by making traction on the uterus towards the opposite side from which we are cutting, the broad ligament can be cut away close to its pelvic attachment, Figs. I and IV.

If one attempts to ligate the artery in the tissues any distance from the uterus without first dissecting it out, there is great danger of including carcinomatous tissue within the ligature and thus defeating the object of the operation.

Another reason for first ligating the artery as far out as possible is that there is no possibility of removing any more tissue after the broad ligament is once divided, as that portion attached to the pelvic wall at once retracts, carrying with it the artery and any carcinomatous tissue which may lie beyond the ligatures. This is the essential principle in the operation which is now proposed, and if followed will unquestionably give better results than where the broad ligament is ligated with one or two ligatures *en masse* and cut away close to the uterus.

While the introduction of the bougies is highly essential to this operation, it can be performed, but with much less facility, by following the course pursued on one side in Case I.

The bougie was not introduced in the right ureter for reasons stated further on, and when the enucleation was begun it was found necessary to dissect out the ureter in its course and draw it to one side with a loose traction ligature, after which the operation was completed with as much ease as on the side where the bougie was introduced.

This necessarily requires more time, and consequently it should be the invariable rule to lay bougies in both ureters, as the operation must be done with the most painstaking care if it is to be of any more value than the methods now pursued.

The details of the operation will be given in the description of the cases, and in the remarks following Case I defective points in the *technique* are noted which are corrected in Case II.

Case I.—Mrs. J. P., mulatto, aged 48 years, admitted April 24, 1895.

Complaint—Hemorrhage from uterus and offensive vaginal discharge.

Marital History—Married 25 years; 12 children; no miscarriages. All labors normal except the last in November, 1894; child still-born. Menses began when she was 14 years of age; flow always regular and painless, lasting one and a half days. Since the birth of her last child she has had almost constant hemorrhage.

Leucorrhœa for many years; up to six months ago the discharge was odorless, but at that time became very profuse and offensive.

Family History—Negative.

Personal History—Patient has always been a very healthy woman.

Present Ailment—In August, 1894, when patient was about six months pregnant, the leucorrhœal discharge above noted became very offensive and irritating, and she began to grow weak and lose flesh. November 16th, 1895, she gave birth to a still-born child, and about one month later had a copious hemorrhage from the vagina, which has continued more or less up to the time of her admission to the hospital. She has at no time suffered the slightest pain, and barring the weakness and general debility, which is more apparent to her friends than herself, feels very well. Urination normal, bowels costive, no pain during defecation. Patient is anæmic and has lost considerable flesh. Appetite poor, sleeps moderately well.

Examination—Abdominal walls lax and flabby, numerous linea albicantes. Vaginal outlet much relaxed; beginning on the vaginal wall 2½ cm. from the cervix there is a fungating mass which almost fills the vagina and completely involves the cervix. The broad ligaments are slightly involved close to the uterus. The fundus uteri is slightly enlarged and freely movable. Appendages normal.

Diagnosis—Cancer of upper portion of vagina and cervix.

Operation, April 26, 1895—Urethra anæsthetized with cocaine, and ureteral bougie inserted into the left ureter through a No. 8 vesical speculum. The patient being very nervous, and as the right broad ligament seemed quite free, it was deemed best to proceed at once with the general anæsthetic, only a slight attempt having been made to lay a bougie in this side, which was not successful. An incision 15 cm. in length in the median line exposed the pelvic organs, which were found as described in the examination. The bougie in the left ureter could be felt as a solid cord running up along the side of the cervix and then curving gently outward in company with the iliac vessels and up over the brim of the pelvis. At the base of the broad ligament it lay at least 1½ to 2 cm. outside of the indurated area, and could easily be displaced 1 cm. further out towards the pelvic wall, thus throwing it entirely out of the carcinomatous process.

The operation was begun by tying the upper portion of the left broad ligament, including the ovarian artery, as closely to the pelvic wall as possible, clamping the uterine side and cutting between.

Having divided the round and the upper portion of the broad ligaments, and separated the two layers of the latter, the vesical peritoneum was snipped with the scissors, following the crease where it is reflected onto the uterus, around the anterior

* The Johns Hopkins Hospital Reports, Vol. IV, No. 6.

face of the uterus to the opposite broad ligament. By spreading the layers of the broad ligament apart with a stalk sponge the uterine artery was exposed in the intraligamentary cellular tissue, it appearing somewhat tortuous, and near the uterus imbedded in carcinomatous tissue. A careful dissection was now begun, an assistant in the meantime making strong traction with a small vulsellum forceps caught in the fundus, thus enlarging the normal space between the uterus and pelvic wall and making the artery taut.

The artery was bared for 2½ cm. from the uterus, the dissection being carried well down towards the internal iliac artery, which could be seen pulsating close to the point of ligation. A small blunt-pointed curved aneurism needle proved of great service in carrying the ligature. As the vessel walls seemed somewhat atheromatous, a second ligature was placed for double security. This step in the operation was rather difficult on account of the close proximity to the large vessels, which were in danger of injury. During this dissection the ureter was constantly under touch, thus eliminating all possibility of injuring it.

The ureter was next dissected out of its bed and pushed toward the pelvic wall; and the broad ligament and the intraligamentary tissue ligated on the pelvic side close to the internal iliac vessels, with imbricated ligatures, each including 1 cm. of tissue.

Having reached the vaginal vault, the dissection was carried down along the lateral and anterior vaginal walls with the fingers, by means of which the walls were pushed away from their attachments. There had not been the slightest loss of blood up to this point.

The upper portion of the opposite broad ligament was now ligated on the pelvic side and clamped on the uterine side and cut. The two layers were then separated with a stalk sponge, the uterine artery dissected out and doubly ligated. At this point careful palpation showed the broad ligament to be more extensively involved than the preliminary examination had indicated, and in order to remove as much as possible it became necessary to know the exact position of the ureter lest it inadvertently be ligated or cut.

With the other ureter as a comparative landmark, this ureter was easily located in the broad ligament and dissected out. A loose traction ligature was then thrown around it, and while the dissection was being carried down back of the vaginal walls, was drawn out of the way by an assistant. The broad ligament was ligated close to the pelvic wall as on the opposite side and cut. At this point it became evident that the carcinomatous process had not only penetrated the posterior vaginal wall, but had involved the anterior rectal wall to a considerable extent.

On account of the close relation of the rectal and vaginal walls which were bound together by the inflammatory process, an assistant was directed to insert his index-finger into the rectum while an attempt was made to separate the two walls. This could not be accomplished satisfactorily. The recto-uterine reflection of peritoneum had been previously snipped and pushed off in the same manner as the vesico-uterine reflection. By making strong upward traction on the uterus, the vagina was also drawn upward and made quite tense. By light percussion, a procedure suggested by Dr. Kelly to be employed in all cases of hysterectomy for accurately distinguishing the cervico-vaginal juncture, the point for amputation can be located accurately. An opening was made in the anterior vaginal wall with the sharp-pointed scissors, and from this point the vagina was encircled by an incision made with Dr. Kelly's special hysterectomy spud, which proved of great value here in cutting so deep in the pelvis. Unfortunately a small area of carcinomatous tissue on the rectum could not be removed. With this exception the enucleation seemed to be very thorough. Considerable bleeding from the vaginal walls, which required several ligatures to control it, followed the amputation of the vagina. Before completing the operation another attempt was made to clear the rectal wall of the carcinomatous tissue by a careful dissection, but proved impossible. One or two large strips of iodoformized gauze were packed down into the space occupied by the cervix and upper portion of the vagina, after which the pelvic cavity was closed by whipping together the recto-uterine and vesico-uterine reflections of peritoneum by a continuous suture, beginning at the stump of one ovarian artery and running across to the opposite stump, thus effectually closing off the peritoneal cavity, which was then irrigated with 1 litre of normal salt solution (Fig. V). The abdominal wound was closed with buried silver wire and subcutaneous catgut.

The vaginal gauze was removed in five days. Patient discharged in 24 days. Examination at this time as follows: Vaginal vault smooth and vaulted, small line of cleavage felt where the vaginal walls have united. No sign of local recurrence of the disease.

The pathological examination had by this time been made by Dr. Cullen, who confirmed the clinical observation that all of the carcinoma had not been removed, consequently the patient was requested to return in one month for examination.

June 20—Patient examined to-day, and on the anterior rectal wall there is a minute area which is unquestionably carcinomatous. The patient is perfectly comfortable, has gained five pounds, the hemorrhages have not appeared and she believes she is perfectly well. The pelvis appears to be free, and by rectum there is no trace of induration on either side.

Remarks.—While the dissection of the ureter in which no bougie was introduced was satisfactorily accomplished, it was much slower than on the opposite side, and in contrast much more difficult. The bleeding from the vaginal walls following the excision of the uterus should be obviated by first perforating with sharp scissors the vagina anteriorly well below the carcinomatous area and then ligating the vaginal wall in small segments and cutting, thus controlling all hemorrhage as the operation proceeds (vid. Case II).

With the exception of the one point on the rectum which could not be removed, the operation was very satisfactory. As far as the question of complete cure is concerned, unfortunately for the patient this is quite as serious as though a much larger area was left.

CASE II.—Mrs. E. Y., German housewife, aged 57 years, admitted June 4th, 1895.

Complaint—Excessive loss of blood from uterus.

Marital History—Married twice, one child and one miscarriage during first marriage, labors easy and not followed by any untoward symptoms. Married 22 years to second husband, during which time she has borne three children and had ten miscarriages. Nothing out of the normal course of events occurred in any of the labors, and no pain or discomfort followed the miscarriages. She was attended in all of her confinements by a German midwife. Menopause occurred in her 47th year, up to that time menses always regular and normal since they first appeared in her 19th year.

Family History—Negative.

Personal History—Patient has always been very strong and healthy since childhood.

Present Ailment—One year ago she began to have a slight leucorrhœal discharge, which continued for six months, when it became blood-tinged; since then it has grown more profuse and hemorrhagic until the present, when it is almost pure blood.

About Easter, 1895, she had a severe hemorrhage, losing about one pint of blood.

General Condition—Slight anæmia, no cachexia, very slight pain in lower part of pelvis, no loss of flesh. Appetite good, bowels regular, no urinary complaint. Heart and lungs normal.

Examination—Vaginal outlet relaxed, faint scar tissue in posterior vaginal wall. Projecting into vagina from cervix there is a fungating mass 2.5x5 cm., which is very friable and bleeds freely during the examination.

The cancerous process seems to be circumscribed and extends only slightly onto the vaginal walls. Fundus uteri small, senile, freely movable, not involved by the carcinoma. Broad ligaments very slightly involved. Ovaries not detected, probably senile.

Diagnosis—Cancer of cervix.

Operation, June 6, 1895—Urethra anaesthetized with cocaine and patient placed in knee-breast posture. After an inffectual search for the ureteral orifices it was considered best to place the patient in the elevated dorsal posture, when they were quickly located and bougies inserted into both.

Especial care was observed in this case as in the preceding to disinfect thoroughly the vagina. The broad ligaments were tied off and the dissection of the artery made in the same way as in the preceding operation.

After freeing the vaginal walls for 2½ cm. below the cervix, the vagina was perforated anteriorly, but instead of at once completing the amputation, a small segment of the vaginal wall was ligated and cut and then another, and so on around the entire circumference, so that by the time the uterus with the upper portion of the vagina had been removed all bleeding was checked.

The operation was completed by packing gauze into the upper part of the vagina and closing the peritoneum over this, making the seat of operation entirely extra-peritoneal. This operation required two hours for its completion, the dissection of the uterine arteries requiring more time than any other step. It was practically bloodless and there was no variation in the patient's pulse from the beginning to the end.

The subsequent notes on the case are as follows:

June 7th—Patient recovered from ether by the time she reached the ward; at that time her pulse was 92, full and strong. She has passed a comfortable night. Temperature 99½° F.; pulse 100 this morning.

June 9th—Bowels moved thoroughly from the effects of fractional doses of calomel and an enema. Feels well; no tenderness or distension in abdomen.

June 10th—Gauze pack removed from vagina; no odor; slightly blood-stained.

June 18th—Temperature normal; abdominal wound inspected; subcutaneous catgut absorbed, union perfect, line of incision represented by only a faint hair-line.

July 5th—Patient discharged, feeling perfectly well. Highest temperature on fourth day 100° F.; pulse 112. The vaginal vault is entirely closed in, is perfectly smooth and dome-like. The line of union between its walls is represented by a small, almost imperceptible cicatrix. No induration in the lateral pelvic walls. Prognosis as to radical cure good.

August 30th—Patient returns to-day by appointment; again examined and same condition found as just noted.

In conclusion, the steps of this operation may be summarized as follows:

1. Insert bougies under the local effects of cocaine, thus saving time and conserving the patient's vital powers for the operation.

2. Make abdominal incision of sufficient length to insure free manual movements.

3. Ligate upper portion of broad ligament with ovarian artery; divide vesico-uterine peritoneum around to opposite side; push bladder off, and spread layers of ligament apart, exposing uterine artery.

4. *Dissect uterine artery out for 2½ cm. from uterus beyond its vaginal branch and tie.*

5. Dissect ureter free in the base of the broad ligament.

6. Ligate remainder of broad ligament close to iliac vessels and cut it away from its pelvic attachment.

7. Carry dissection well down below carcinomatous area, even though cervix alone seems to be involved.

8. Proceed on the opposite side in the same manner as on the first side.

9. Perforate vagina with sharp-pointed scissors, making strong traction on uterus with small vulsellum forceps so as to pull the vagina up and make its walls tense, then ligate in small segments (1 cm.), and cut each segment as it is tied.

10. Insert iodoformized gauze from above into raw space left by the hysterectomy; draw vesical and rectal peritoneum over this with a continuous fine silk suture.

11. Irrigate pelvic cavity and close abdomen without drainage.

July 15, 1895.

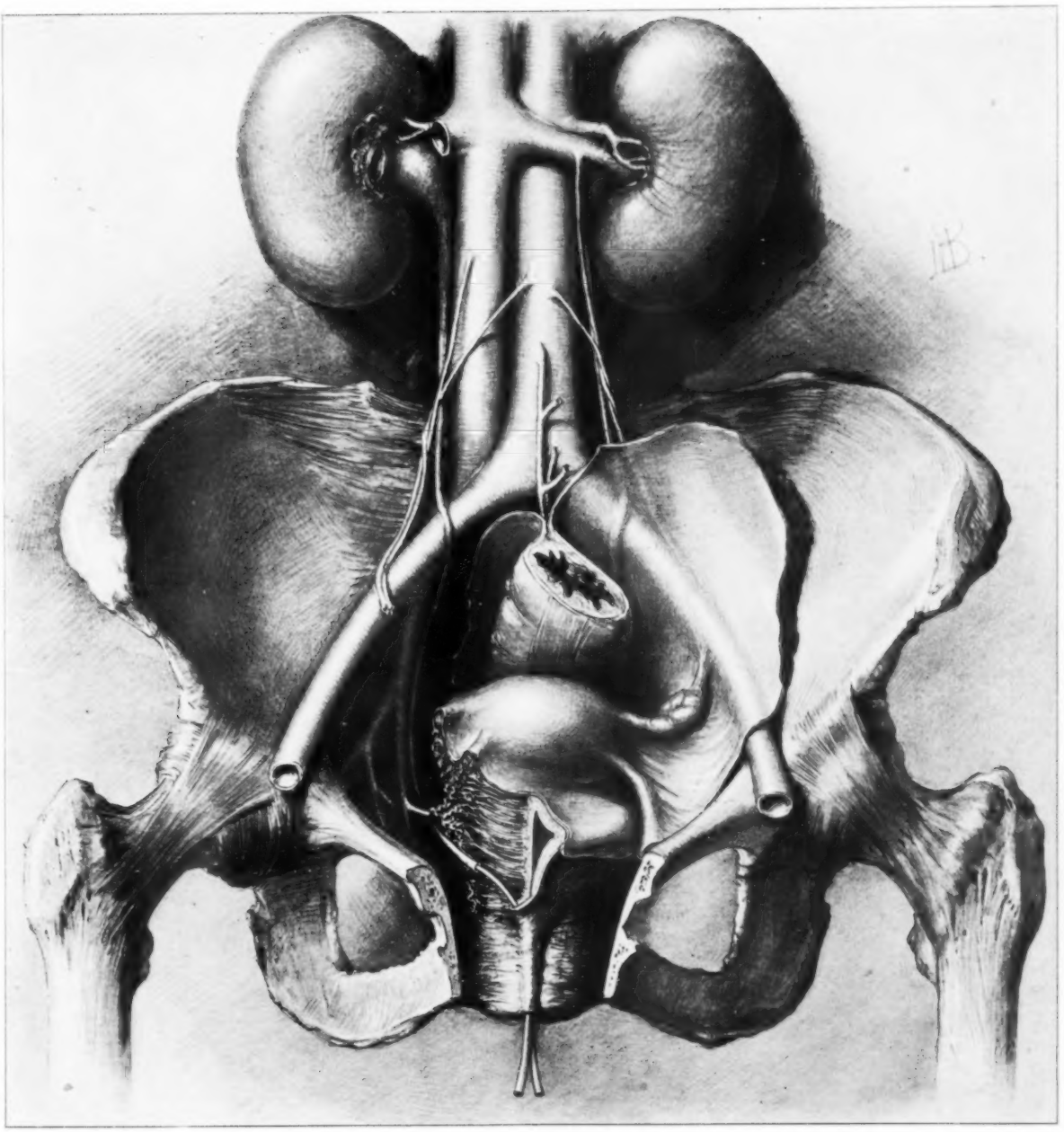

FIG. I.

In this plate the peritoneum of one side of the pelvis is dissected off, showing the intimate anatomical relation of the bladder, uterus, uterine artery and ureter. Bougies are inserted into the ureters making them stand out as rigid tubes. The close relations of uterine artery and ureter and the ureter and cervical portion of uterus are well demonstrated, showing the impossibility of a wide excision of the broad ligaments without the introduction of the bougies into the ureters.

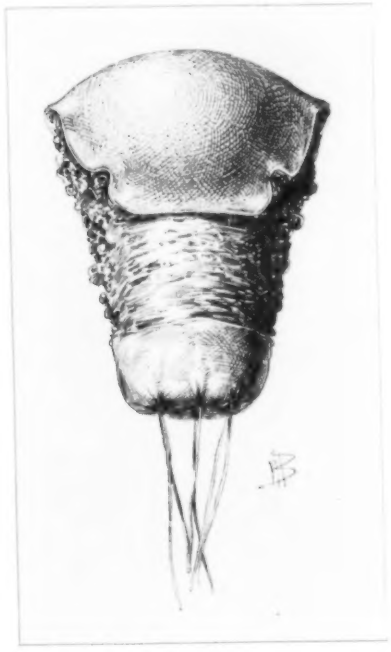

FIG. III.

Uterus removed by vaginal hysterectomy, none of the broad ligaments or vagina excised with it.

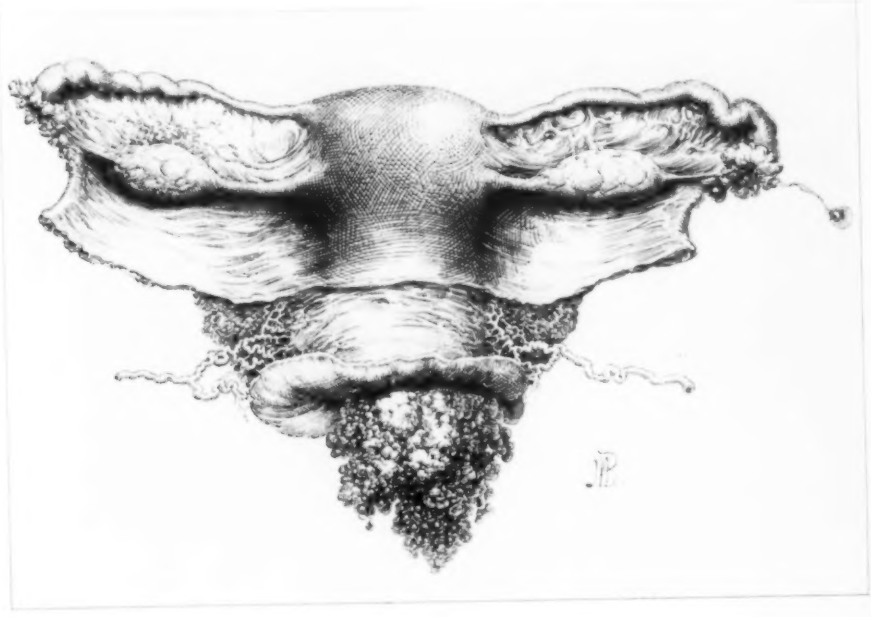

FIG. IV.

Uterus removed from Case II., showing the uterine artery as dissected out before the broad ligaments were freed from their pelvic attachments. The major portion of the broad ligaments and a considerable cuff of vagina were excised with the uterus *en masse*.

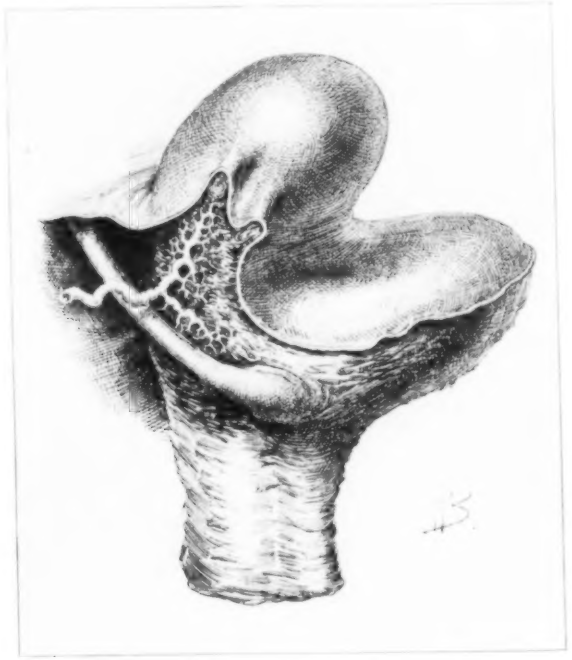

FIG. II.

Peritoneum dissected off, giving a lateral view of the uterus and bladder with their relations to the uterine artery and ureter and the latter vessels to each other. The impossibility of removing any of the broad ligament without great danger of cutting or ligating the ureters is perfectly demonstrated in this plate.

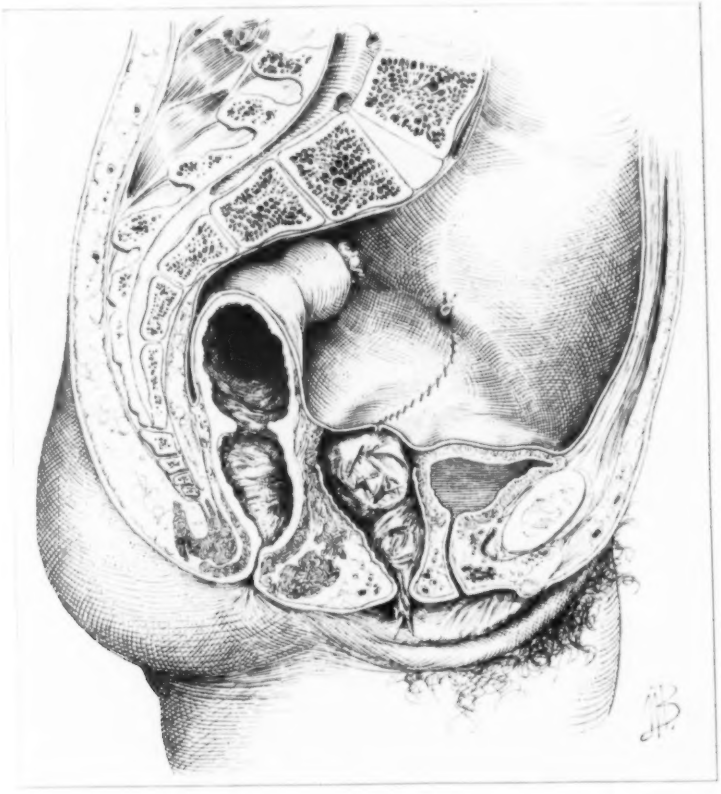

FIG. V.

Operation as it appears when completed. The space left by the removal of the uterus is filled with gauze from above, after which the vesical and rectal peritoneum are whipped over it with a continuous suture of fine silk, beginning at one ovarian stump and running across to the opposite stump.

NOTES ON NEW BOOKS.

Laboratory Guide for the Bacteriologist. By LANGDON FROTHINGHAM, M. D. V. (*Philadelphia: W. B. Saunders*, 1895.)

This little book is arranged and written for purposes of easy reference in laboratory work. It consists of a preliminary chapter on bacteriological technique, and a collection of the more common formulæ for the making of media, staining, etc.

The chapter on bacteriological technique is short and clear, and gives many little hints which are usually picked up by bitter experience and are not found in the ordinary text-book.

The formulæ are satisfactorily arranged, the chief objection to their rapid use being the constant occurrence of foot-notes referring back to previous formulæ or parts of previous formulæ.

Book of Detachable Diet Lists, for Albuminuria, Anæmia and Debility, Constipation, Diabetes, Diarrhœa, Dyspepsia, Fevers, Gout or Uric Acid Diathesis, Obesity, Tuberculosis, and a Sick Room Dietary. By JEROME B. THOMAS, M. D. (*Philadelphia: W. B. Saunders*, 1895.)

This book contains a set of ten lists of articles of food adapted to the various conditions named above. The dietary is printed upon the back of the physician's prescription, and the list of articles is a liberal one from which to select. As an aid to the physician's memory of available articles of food when arranging a dietary, the lists are very valuable. They will suggest a variety in diet which cannot but be helpful to the patient. The lists being perforated and easily detached, it will be practicable for the nurse to have before her constantly a scheme of feeding. They will be most useful.

A System of Surgery. Edited by FREDERIC S. DENNIS, M. D., etc. assisted by JOHN S. BILLINGS, M. D., etc. (*Philadelphia: Lea Bros. & Co.*, 1895.)

The first volume of this system opens with a section on the History of Surgery, from the pen of Dr. John S. Billings. This section contains a history of the surgical art from the time of Egyptian surgery to that of the present day. On account of the immense amount of material there is necessarily an encyclopædic character imparted to certain of the work, but the full descriptions of the works and methods of the more important surgical writers, and the introduction of numerous descriptions of surgical procedures and quotations from the more interesting works, make the article very interesting reading. The description of the American surgeons is full and interesting and doubtless the most complete yet published. The section ends with a list of the prominent surgical journals.

The article on surgical pathology, by Dr. Councilman, is a clear and concise presentation of the subject. The chapter on inflammation is especially to be recommended; it is well, though diagrammatically illustrated, and is a clear and up-to-date exposition of the subject. The article on tuberculosis and tubercle is also well worthy of attention.

Dr. Welch's article on the general bacteriology of surgical infections is well arranged and clearly written. It embodies the results of a large personal experience and an extensive knowledge of the literature. The article takes up the bacteria normally inhabiting the body which may be concerned in surgical diseases, their methods of introduction and elimination, and the processes which favor their growth and action in the body. An excellent summary of the leading bacteria of surgical infections and their biological properties concludes the article.

The section by Dr. Nancrede on symptoms, diagnosis and treatment of inflammation, abscess, ulcer and gangrene, contains besides an excellent article on wounds, an article on one of the newest surgical affections, traumatic hysteria. Why articles on diaconti-asis and mycetoma should be introduced into this section we utterly fail to see.

Dr. Carmalt's article on septicæmia and pyæmia, Dr. Warren's on traumatic fever, erysipelas and tetanus, and Dr. Biggs' on hydrophobia, are all well written and satisfactory.

The article of Dr. Conner on gunshot wounds is an excellent one. It contains an excellent account of the effects caused by the modern forms of weapon with the new projectiles, with excellent illustrations, mostly from the article of Dr. LaGarde.

The article on fractures is by the Editor. It is well written and conservative, and contains a good many excellent illustrations from natural preparations. It also contains a good many illustrations of antique surgical appliances and refined instruments of torture, such as "Malgaigne's hooks," which had better have been left out of a text-book on modern surgery.

Dr. W. C. Wood's article on anæsthesia will well repay reading. It contains a full account of the theoretical bearings of the subject and many useful and important practical points.

Dr. Gerster's article on antiseptic and aseptic surgery is, as we should have expected, a thorough one. We are inclined to think, however, that a much more convenient and comfortable operating habit than a long apron and sabots could be found, without sacrificing cleanliness.

The volume closes with a good article on operative surgery, by Dr. Stephen Smith.

As a whole the volume is a decided success. It is well printed on good paper and the illustrations are well executed. We hop that the succeeding volumes will be as good as this one.

NOTICE.

All inquiries concerning the admission of free, part pay, or private patients to the Johns Hopkins Hospital should be addressed to Dr. Henry M. Hurd, the Superintendent, at the Hospital.

Letters of inquiry can be sent, which will receive prompt answer, or personal interviews may be held.

Under the directions of the founder of the Hospital the free beds are reserved for the sick poor of Baltimore and its suburbs and for accident cases from Baltimore and the State of Maryland. To other indigent patients a uniform rate of $5.00 per week has been established. The Superintendent has authority to modify these terms to meet the necessity of urgent cases.

The Hospital is designed for cases of acute disease. Cases of chronic disease are not admitted except temporarily. Private patients can be received irrespective of residence. The rates in the private wards are governed by the locality of rooms and range from $20.00 to $35.00 per week. The extras are laundry expenses, massage, the services of an exclusive nurse, the services of a throat, eye, ear and skin or nervous specialist, and surgical fees. Wherever room exists in the private wards and the condition of the patient does not forbid it, companions can be accommodated at the rate of $15.00 per week.

One week's board is payable when a patient is admitted.

THE MALARIAL FEVERS OF BALTIMORE.

An Analysis of 616 cases of Malarial Fever, with Special Reference to the Relations existing between different Types of Haematozoa and different Types of Fever.

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